

UNITED STATES DISTRICT COURT
FOR THE
DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE)	
COMPANY, JOHN HANCOCK)	
VARIABLE LIFE INSURANCE)	
COMPANY, and MANULIFE INSURANCE)	
COMPANY (f/k/a INVESTORS)	
PARTNER LIFE INSURANCE)	
COMPANY),)	CIVIL ACTION NO. 05-11150-DPW
)	
Plaintiffs,)	
)	
v.)	
)	
ABBOTT LABORATORIES,)	
)	
Defendant.)	

AFFIDAVIT OF STEPHEN J. BLEWITT

I, Stephen J. Blewitt, hereby state under oath that:

1. My name is Stephen J. Blewitt. I reside in Reading, Massachusetts.
2. I am a Senior Managing Director of plaintiff John Hancock's Bond and Corporate Finance Group ("BCFG"). I have been called to testify in this action concerning my involvement in negotiating, evaluating and administering the written "Research Funding Agreement" that John Hancock entered into with defendant Abbott Laboratories ("Abbott") on March 13, 2001 (the "Research Funding Agreement" or the "Agreement"). This affidavit sets forth my direct trial testimony.

3. I previously have submitted affidavits to this Court both in this action and in the prior, related action titled John Hancock Life Insurance Company, et al. v. Abbott Laboratories, Civil Action No. 03-12501-DPW (“Hancock I”). For the convenience of the Court, I have repeated the relevant portions of those documents in this affidavit.

The Parties and My Background

4. Plaintiff John Hancock Life Insurance Company is a company, duly formed and existing under the laws of the Commonwealth of Massachusetts, that provides various insurance and investment products to retail and institutional customers. John Hancock Life Insurance Company also is an investor in a diversified portfolio of investments, including commercial loans, corporate bonds, public and private securities and various other types of investment vehicles. John Hancock’s investments are intended, *inter alia*, to ensure that the company generates a sufficiently stable stream of income to meet John Hancock’s payment obligations to its policy holders, shareholders, and investors.

5. Plaintiff John Hancock Variable Life Insurance Company (“JHVL”) is an affiliated company of John Hancock Life Insurance Company, duly formed and existing under the laws of the Commonwealth of Massachusetts. JHVL provides variable life insurance products that link life insurance coverage and an investment return to an underlying portfolio of investments selected by the policyholder.

6. Plaintiff Manulife Insurance Company (“Manulife”) is an insurance company duly formed and existing under the laws of the State of Delaware. Prior to approximately February 2005, Manulife was known as “Investors Partner Life Insurance Company.” Manulife is a wholly-owned subsidiary of JHVL that sells various types of life insurance products.

7. Unless otherwise indicated, plaintiffs John Hancock Life Insurance Company, JHVL and Manulife are collectively referred to herein as “John Hancock” or “Hancock.”

8. I attended the University of Chicago and graduated with a Bachelors Degree in Economics in 1982. I began work with John Hancock shortly after my graduation from the University of Chicago. While employed by John Hancock, I attended graduate school at Boston University, and ultimately obtained a Masters Degree in Business Administration from Boston University in 1987.

9. My first position with John Hancock was in Hancock’s Group Pensions Department. In 1988, I joined Hancock’s BCFG, which serves as the primary fixed income asset manager for John Hancock, as well as for various third parties. I started with the BCFG as an Investment Officer and subsequently received a series of promotions within that group. As of 2000-2001, I was a Managing Director of John Hancock’s BCFG. My duties included seeking out new, favorable investment opportunities for Hancock. My immediate supervisor in that time frame was Roger Nastou.

John Hancock’s Prior Investments in the Pharmaceutical Industry

10. Prior to 2000, John Hancock had made other investments in the pharmaceutical industry. Hancock’s investments took different forms; some were equity investments and some were debt investments.

11. For example, in or around 1997, John Hancock made a \$32 million equity investment in Metabolex, Inc. (“Metabolex”), a company that focused on the discovery and development of new treatments for diabetes and related diseases. Abbott was another investor in Metabolex, and the terms of John Hancock’s investment included the right to “put” or require Abbott to buy out Hancock’s interest at a later time. The proceeds from Hancock’s

investment were used by Metabolex to help fund research and development of a combined Abbott/Metabolex drug discovery program over a three year period.

12. I was a Senior Investment Officer for John Hancock on the Metabolex transaction. As part of the transaction, Metabolex was required to make certain representations and warranties to John Hancock. I and others at John Hancock also performed some targeted due diligence with respect to the potential markets for new diabetes treatments prior to recommending the Metabolex investment. Our work included a general analysis of the overall market using various industry research reports. We also engaged a scientific consultant (Dr. Allan Haberman) to provide additional independent scientific input and analysis.

13. John Hancock's investment in Metabolex was a successful one. Hancock eventually exercised its right to "put" its investment to Abbott for a gain.

14. In or about 1999, John Hancock made a \$5 million equity investment in Idun Pharmaceuticals, Inc. ("Idun"), a company that focused on the discovery and development of small molecule cancer therapeutics targeting the biological pathways that control "apoptosis," or programmed cell death. Prior to 1999, Idun had entered into an exclusive scientific collaboration in the field of apoptosis with Abbott, which also was an equity investor in Idun. The proceeds from Hancock's investment were used by Idun for working capital and general corporate purposes, including funding continued research and development work.

15. I was a Senior Investment Officer for John Hancock on the Idun transaction. As part of the transaction, Idun was required to make certain representations and warranties to John Hancock. Once again, I and others at John Hancock also performed some targeted due diligence with respect to the potential markets for new cancer drugs prior to recommending the Idun investment. Our work included an analysis of the overall market for cancer therapies

based upon various industry research reports. We also engaged two scientific consultants (Dr. Jay George and Dr. Lynn Klotz) to provide additional independent input regarding the market for cancer drugs and emerging cancer therapies.

16. Pfizer eventually purchased Idun for almost \$300 million dollars.

17. All told, John Hancock made investments totaling more than \$180 million in a series of pharmaceutical or pharmaceutical-related entities prior to 2000, including Metabolex, Idun and various other entities such as Purdue Pharma, L.P., Celegene Corporation, Elan Pharmaceutical Investments Ltd., and Pharma Marketing Ltd. In each instance, John Hancock requested and received representations and warranties regarding the investment; in each instance, John Hancock personnel performed targeted due diligence concerning the products and/or the potential markets.

The Negotiation of the Research Funding Agreement

18. The negotiations between John Hancock and Abbott that ultimately resulted in the Research Funding Agreement that forms the basis of this action began sometime in or around late 1999. I am the person at John Hancock who had primary responsibility for evaluating, negotiating and administering that investment on Hancock's behalf.

19. Prior to the commencement of negotiations concerning the Research Funding Agreement, I had developed a business relationship with Philip Deemer, then the Director of Abbott's Corporate Licensing Department, as a result of John Hancock's prior joint investments with Abbott in Metabolex and Idun. Mr. Deemer and I periodically spoke with one another. Our discussions eventually focused on a potential investment by John Hancock in a selected portfolio of pharmaceutical compounds being developed by Abbott. At some point

in time, Stephen Cohen, then the Controller for Abbott's Pharmaceutical Research and Development Division, became involved in the discussions as well.

20. I was not the only person at John Hancock involved in the development, evaluation and approval of the proposed deal with Abbott. I was assisted at various times by, among others, Scott Hartz, who then was a Managing Director and Head Portfolio Manager in the BCFG, as well as by Shannon Walsh, a Portfolio Analyst.

21. As explained to me by Mr. Deemer, Abbott was interested in a potential funding agreement with John Hancock, in part, because it offered Abbott the opportunity to supplement its internal research and development budget on what Abbott regarded as reasonably attractive financial terms. I, in turn, was seeking an investment opportunity that would provide above-average returns on a portion of John Hancock's total investment portfolio with a reasonable level of risk.

22. Over time, Mr. Deemer, Mr. Cohen and I began to concentrate our discussions on an investment structure whereby John Hancock would invest approximately \$50 million per year over a four-year period to fund the development of a specified "basket" of pharmaceutical compounds in Abbott's then current research and development portfolio. Abbott, in turn, would compensate John Hancock for its investment through a series of milestone and royalty payments that would become due if and when the compounds were commercialized.

23. I understood during negotiations that John Hancock's ability to earn a return on its investment in the proposed basket of Abbott pharmaceutical compounds would depend on the eventual commercial success of those compounds. If some or all of the compounds failed or otherwise were unsuccessful, John Hancock's financial return would be significantly diminished or eliminated entirely.

24. With these considerations in mind, I expressly notified Mr. Deemer during the negotiation of the Agreement that, from John Hancock's perspective, the structure of the proposed deal was highly dependent upon the number of pharmaceutical compounds included in the transaction, as well as the stage of development and expected sales of each compound. A true and accurate copy of an e-mail message that I sent to Mr. Deemer on the topic, dated March 7, 2000, is attached hereto as PLs' KP.

25. I specifically requested a diversified basket of compounds from Abbott reflecting a variety of therapeutic indications, stages of development, and expected sales in order to provide an acceptable return on John Hancock's proposed investment with a reasonable overall level of risk.

26. In or about mid-2000, I began working with various Abbott personnel, including Mr. Deemer, to identify a suitable basket of pharmaceutical compounds to include in the proposed deal, and to develop a mutually-acceptable royalty payment structure. Among the compounds proposed by Abbott for inclusion in the John Hancock basket were ABT-518, a Matrix Metalloproteinase Inhibitor (MMPI) for the treatment of cancer; ABT-594, a selective neuronal nicotinic (NNR) agonist for the treatment of chronic pain that just was commencing a Phase IIb clinical trial for diabetic neuropathic pain; ABT-773, one of a new class of powerful antibiotics known as "ketolides"; and ABT-980, a selective alpha blocker for the treatment of urinary tract blockages.

27. In negotiating John Hancock's Research Funding Agreement with Abbott, it was my intention to invest only in promising development candidates with positive commercial prospects. Neither I nor, based on my observations, anyone else at John Hancock intended to invest in compounds that Abbott knew or had reason to believe would be discontinued shortly.

28. I and my fellow investment professionals at John Hancock were in no position, however, to independently know the current status, prospects or plans for each of the deal compounds within Abbott's pharmaceutical R&D organization. That is why John Hancock required, with Abbott's agreement, that Abbott formally represent and warrant to Hancock the up-to-date status, condition and plans for the various compounds in the proposed basket of compounds. As set forth in an e-mail message that I sent to Mr. Cohen on July 7, 2000, specific information that John Hancock required in this regard included, among other things,

[c]urrent status of clinical trials (i.e., what is current stage, what were results from prior stage or interim results – specifically, trial design and endpoints, discussions with FDA, Go/NoGo decision points). Potential labeling issues. Potential manufacturing issues. Timeline for completion of trials, NDA filing, [a]pproval. Commercialization rights and freedom to operate. Patent status.

A true and accurate copy of my e-mail to Mr. Cohen, dated July 7, 2000, is attached hereto as PLs' CI.

29. Abbott also agreed to provide to John Hancock information concerning Abbott's anticipated development spending on the proposed compounds in the form of projections and drafts of Abbott's first "Annual Research Plan" ("ARP"). True and accurate copies of various projections that Abbott provided to me in or about the fall of 2000 are attached hereto as PLs' PE and PO. I informed Mr. Deemer that Abbott's expected spending on the proposed compounds was important to John Hancock because I and others at Hancock regarded Abbott's own internal spending plans as a useful barometer of the commercial and technical prospects for the various compounds.

30. In response to John Hancock's requests, Mr. Deemer provided me, in or around June 2000, with a series of draft "Descriptive Memoranda" that included technical, financial

and other information for the compounds in Hancock's proposed basket of compounds. These materials were supplied to John Hancock by Abbott for the explicit purpose of permitting Hancock to understand and evaluate the proposed deal. True and accurate copies of the draft Descriptive Memoranda for ABT-518, ABT-594 and ABT-773 that Abbott provided to John Hancock in that timeframe are attached hereto as Ex. 1, and PLs' CC and HX.

31. Although the format of Abbott's individual Descriptive Memoranda varied somewhat, each Memorandum typically contained, in part: (a) a basic overview of the subject compound that described, among other things, the technical merits and development status of the compound, including the status and/or results of any clinical trials; (b) a discussion of the expected market for the compound, including the specific indications (*i.e.*, conditions or disease states) for which the compound was being developed by Abbott and estimates of the size of the U.S. and ex-U.S. commercial markets for each indication; (c) a description of the nature and severity of any known or suspected side effects and other important "considerations"; (d) an identification of any actual or potential competing products; and (e) a discussion of Abbott's current and future development plans for the compound. Each Descriptive Memorandum was clearly marked "Confidential" by Abbott.

32. At or around the time that Mr. Deemer provided me with the draft Descriptive Memoranda, I retained Dr. Lynn Klotz to assist me in evaluating the compounds that Abbott proposed to include in the deal. Dr. Klotz holds a Ph.D. in Chemistry and has substantial experience and knowledge concerning the pharmaceutical industry and medical issues.

33. I previously had retained Dr. Klotz to help evaluate John Hancock's proposed investment in Idun, and I found his research and analysis regarding the market for cancer

treatments to be very helpful in that context. I believe that I retained Dr. Klotz to evaluate another potential pharmaceutical investment in the same time frame.

34. I retained Dr. Klotz again in mid-2000, but not to comprehensively examine the science behind the compounds in Abbott's proposed basket of compounds. Rather, I retained him to review the descriptions and data contained in Abbott's Descriptive Memoranda and to verify, to the best of his ability using various available sources, the accuracy of the information that Abbott had supplied. Because Abbott had expressed a desire to close its proposed deal with John Hancock within the next few months, I asked Dr. Klotz to undertake and complete his work as soon as possible. A true and accurate copy of an e-mail message that Mr. Deemer sent to me on July 16, 2000, indicating Abbott's desire to move the deal forward promptly, is attached hereto as PLs' KV.

35. Dr. Klotz kept me apprised of his work by telephone and through a series of reports and updates that he sent to me in the months of June and July 2000. True and accurate copies of various reports and updates from Dr. Klotz are attached hereto as PLs' HY, KU, and KY.

36. I and others at John Hancock also employed the information provided by Abbott, in conjunction with general industry data obtained from other sources, to prepare a detailed "Monte Carlo" computer model that we used to develop projections and financial expectations for the proposed deal with Abbott. A Monte Carlo simulation generates numerous possible performance outcomes or scenarios that might occur in the future using a random number generator. It can be designed to account for the uncertainty and performance variation that is found in financial markets. The result of a Monte Carlo simulation is a

probability distribution of portfolio gains and losses that can be used to determine the value and the risk of a portfolio.

37. John Hancock's Monte Carlo simulation entailed running multiple projected scenarios that assessed each Program Compound's commercial and scientific risk profile in order to calculate a combined risk-assessment and expected rate-of-return on John Hancock's total investment, which information was used, in turn, by Hancock to determine what financial terms to demand in the Agreement, as well as whether to enter into the Agreement at all. I and other John Hancock personnel repeated the Monte Carlo simulation using updated data on numerous occasions while negotiations were underway. A true and accurate copy of an example of the output from one of John Hancock's early Monte Carlo simulations for the proposed deal with Abbott is attached hereto as PLs' KQ.

38. Specific data that John Hancock's Monte Carlo simulation considered and analyzed included, among other things: (a) the number of compounds in Hancock's proposed basket; (b) the likelihood that each compound actually would be fully developed by Abbott and obtain regulatory approval; (c) the anticipated commercial launch date for each compound; (d) likely peak and total sales for each compound once launched; (e) anticipated royalty rates; (f) estimates of the milestone and royalty payments that Hancock was likely to receive on both an annual and an aggregate basis; (g) Hancock's estimated risk of loss on the transaction; and (h) Hancock's estimated annual rate of return on the transaction.

39. In many instances, John Hancock's Monte Carlo simulation incorporated more conservative projections than those provided by Abbott in the draft Descriptive Memoranda and other materials provided to Hancock by Abbott, including lower peak sales projections for the proposed compounds.

40. The results of John Hancock's Monte Carlo simulation indicated that, assuming the underlying data concerning the condition of, and prospects for, the compounds was reasonably accurate, the proposed deal could be expected to generate average annual returns to Hancock in the range of approximately eighteen to twenty-two percent (18-22%), with a risk of total loss of approximately one to two percent (1-2%). These values were acceptable to me and caused me to continue to pursue the proposed transaction with Abbott. Under our method of analysis, however, the elimination of even a single compound from the basket would have had a significant, adverse impact on the results of the analysis and the attractiveness of the deal from my perspective and, I believe, from the perspective of John Hancock's management.

41. I notified Abbott during negotiations of John Hancock's expected returns on its investment with Abbott. On March 7, 2000, I forwarded to Mr. Deemer and Mr. Cohen a draft Summary of Terms. In my accompanying e-mail message, I stated, in part, that,

[w]e believe that a diversified basket of compounds should yield the investor an IRR of 20-25%. Based on your desire to reduce the cost of capital and our desire to lower our risk, we have built in milestone payments, a tiered royalty structure, and a termination date for the royalties. The model provides us with an expected yield of 18-22%.

A true and accurate copy of my e-mail to Mr. Deemer and Mr. Cohen and attached Summary of Proposed Terms, dated March 7, 2000, is attached hereto as PLs' KP.

42. After Dr. Klotz had completed his independent research in mid-July 2000, he and I participated in a telephone interview of Dr. John Leonard of Abbott on or about July 28, 2000, during which Dr. Klotz asked Dr. Leonard, Abbott's Vice President of Development, a series of questions concerning the various proposed compounds. Mr. Deemer and Mr. Cohen also participated in that telephone interview. Dr. Klotz took notes of Dr. Leonard's responses

to each question during the telephone conference and prepared a written summary of his responses shortly thereafter. A true and accurate copy of that interview summary with Dr. Klotz's cover e-mail message to me, dated July 28, 2000, is attached hereto as PLs' KY.

43. During the course of the interview, Dr. Klotz specifically questioned Dr. Leonard about, among other things, the potentially small therapeutic window (*i.e.*, the ratio between the minimum dosage necessary to treat the indicated disease effectively and the maximum safe or tolerable dosage) of ABT-594, and asked him whether Abbott regarded it as acceptable. As I recall, Dr. Leonard responded in part by stating, in words or in substance, that when Abbott gave patients the "upper-limit dose" of ABT-594, "the side-effects aren't dangerous: headache, vomiting," and that these "minor side effects" appeared "to go away over time."

44. Based on his independent review of the publicly-available literature, his discussions with various researchers and physicians, and our telephone interview with Dr. Leonard, Dr. Klotz informed me in late July 2000 that, as best he could tell, there was "no indication of any deception on Abbott's part" with respect to the information provided in Abbott's draft Descriptive Memoranda, and that he did not see any reason for John Hancock not to move forward with its proposed investment in those compounds. Dr. Klotz's e-mail message to me containing his recommendation is included in PLs' KY.

45. I understood that Dr. Klotz remained available to further consult with me regarding John Hancock's proposed deal with Abbott after July 2000. I did not ask Dr. Klotz to do so, however, because I did not become aware of any new information from Abbott after that date that I believed required Dr. Klotz's further review or analysis.

46. Negotiations over the specific terms of the proposed Agreement between John Hancock and Abbott continued into the fall of 2000. John Hancock was represented in those negotiations by me, by attorneys W. Brewster Lee and Kevin Tormey of the law firm of Choate, Hall & Stewart in Boston, and by one of John Hancock's in-house attorneys, Amy Weed. Abbott was represented by Mr. Deemer and by its in-house attorneys, Daphne Pals and Brian Smith. Abbott prepared the first draft of the Research Funding Agreement, which Mr. Deemer forwarded to me on August 17, 2000. A true and accurate copy of an e-mail to me from Mr. Deemer with the first draft attached, dated August 17, 2000, is attached hereto as PLs' LC. A true and accurate copy of an example of another draft Agreement that was exchanged between the parties in October 2000 is attached hereto as PLs' LI.

47. By September 2000, the basic terms of the proposed transaction with Abbott had solidified to the point that it was possible to submit the deal to John Hancock's management for approval in concept. John Hancock's internal procedures at the time required the approval of Hancock's Bond Investment Committee, as well as its Committee of Finance, before a deal of the size that we were considering with Abbott could be finalized.

48. In September 2000, I prepared a report summarizing the proposed terms and the business rationale for the contemplated deal with Abbott (referred to internally and in this affidavit as a "Yellow Report") for submission to John Hancock's Bond Investment Committee and to the Committee of Finance. According to John Hancock standard practices at the time, the Yellow Report served as the principal, if not the only, document that Hancock's Bond Investment Committee and Committee of Finance reviewed in considering the Abbott transaction. A true and accurate copy of that Yellow Report, dated September 21, 2000, is attached hereto as PLs' LF.

49. I drafted the Yellow Report with the assistance and input of Mr. Hartz in reliance, to a large extent, on the information concerning the compounds that John Hancock had received from Abbott, on our Monte Carlo simulation, on the evaluation performed by Dr. Klotz, and on information obtained from various publicly-available sources. I believed at the time that the information contained in the Yellow Report was reasonably accurate, and that the assumptions and projections included in the Yellow Report were realistic and reasonably conservative.

50. The Yellow Report for the proposed Abbott transaction states, in part, that,

[w]e are recommending a \$220 million commitment to fund research and development expenses for a basket of eight pharmaceutical products ("Program Compounds") currently under development by Abbott Laboratories ("Abbott")....

The Program Compounds are a diversified pool of eight compounds owned by Abbott Laboratories and in various stages of clinical development. The Compounds are divided between late-stage and early-stage, including three Phase III, two Phase II, one Phase I, and two pre-clinical compounds. The compounds are well-diversified from a disease/stage perspective, although several compounds are focused on the cancer market.... During the term of the transaction, we expect Abbott to spend approximately \$1.3 billion (including John Hancock's commitment) on further research and development for the Compounds.

Through the management fee and anticipated milestone payments, we expect to generate at least an 8% return on investment during the initial four years of the transaction. The average return is approximately 17.5% over 15 years. If we assume that we could sell our future royalty stream after the fifth year, our average five-year IRR would be about 22%.

The transaction is structured to provide a one-to-two percent probability of total loss combined with a one-to-two percent chance of not earning a return. This is approximately equivalent to a 60 basis point annual loss over five years – or a "Ba1" credit

rating. The expected return of 17.50% is attractive relative to the risk of the transaction.

51. I presented the proposed Abbott transaction to John Hancock's Bond Investment Committee on September 21, 2000. In the course of the presentation, I was asked various questions concerning the proposed structure of the transaction, the risk of the transaction, and the expected return for John Hancock on the transaction. The Bond Investment Committee ultimately voted to approve the deal based on, and as recommended in, the Yellow Report.

52. Roger Nastou, then the head of John Hancock's Bond and Corporate Finance Department, subsequently presented the Yellow Report for the proposed Abbott transaction to Hancock's Committee of Finance on October 10, 2000. After some discussion, the Committee of Finance also voted to approve the deal based on, and as recommended in, the Yellow Report. A true and accurate copy of the relevant minutes of the Committee of Finance, dated October 10, 2000, is attached hereto as PLs' LG.

53. Having obtained approval for the proposed transaction with Abbott from John Hancock's Bond Investment Committee and Committee of Finance, I and the others working on the deal were able to go forward with finalizing the terms of the deal and getting it executed. That process, however, took considerably longer than I had anticipated due to a variety of events.

54. One principal reason for the delay was Abbott's decision in the fall of 2000 to terminate the development of ABT-980, one of the compounds in John Hancock's planned basket of compounds. Mr. Deemer informed me that Abbott had decided to discontinue the development of ABT-980 in late October 2000. A true and accurate copy of an e-mail from

Mr. Deemer to me discussing Abbott's decision, dated October 27, 2000, is attached hereto as PLs' LJ.

55. The news regarding ABT-980 caused me considerable concern. The elimination of just that one compound from the portfolio materially altered the economics and attractiveness of the proposed deal from John Hancock's perspective. It reduced John Hancock's expected return and increased Hancock's risk of total loss. In light of the changes resulting from Abbott's decision to terminate ABT-980, I informed Mr. Deemer that John Hancock no longer was willing to proceed with the contemplated Agreement on the terms then proposed.

56. Rather than abandoning the proposed transaction entirely, however, the parties attempted to compensate for the loss of ABT-980 by significantly altering, among other things, the timing and amount of Hancock's proposed investment, as well as the milestones that would trigger Hancock's payment obligations. A true and accurate copy of a proposed draft Agreement incorporating the revised deal structure and terms, dated November 16, 2000, is attached hereto as PLs' LL. Several draft agreements incorporating the modified deal structure were exchanged between the parties in November and December 2000.

57. In or around December 2000, I was told by Mr. Deemer that Abbott's management wished to put its proposed transaction with John Hancock "on hold" because they were preoccupied with Abbott's recent acquisition of Knoll Pharmaceuticals ("Knoll"). I since have learned from documents produced by Abbott in this litigation that Abbott actually put the proposed transaction with John Hancock "on hold" in late 2000 because Abbott's management was "less enthusiastic about moving forward due to the new deal structure," and that Abbott's management simply "want[ed] to postpone a final decision until the new year." A copy of an

internal memorandum to that effect from Mr. Deemer to Arthur Higgins, then the President of Abbott's Pharmaceutical Products Division, dated December 1, 2000, is attached hereto as PLs' LO.

58. In or about mid-January 2001, I was notified that Abbott's management wished to proceed with the proposed transaction on the terms that existed as of October 2000, and that Abbott was willing to compensate John Hancock for the loss of ABT-980 by adding additional compounds to the planned basket of compounds.

59. I reviewed several new compounds that Abbott proposed to add to John Hancock's basket of compounds. One of the compounds that Abbott proposed to provide as a replacement for ABT-980 was ABT-822, a bimoclomol compound for the treatment of diabetes. I promptly reviewed the available information concerning bimoclomol compounds and concluded that they were not sufficiently promising to warrant an investment by John Hancock. Accordingly, I declined Abbott's offer to replace ABT-980 in the proposed Agreement with ABT-822.

60. Two additional compounds that Abbott proposed to add in place of ABT-980 were ABT-510 and ABT-492. I was provided with information on each compound by Abbott. I reviewed the information from Abbott and other available information on the compounds and determined that ABT-510, a cytotoxic compound intended to inhibit the growth of new blood vessels in cancerous tumors, was similar to some of the cancer therapies that Drs. Klotz and George previously had evaluated at my request for the Idun deal. Based on my existing knowledge of the market for such therapies and the fact that the proposed Agreement with Abbott provided that Hancock would receive a replacement compound if the first of ABT-510

and ABT-492 did not progress in clinical trials, I did not perceive a need to reengage Dr. Klotz to evaluate that compound.

61. My research further disclosed that ABT-492 was an anti-infective agent that Abbott recently had in-licensed from Wakunaga Pharmaceutical Co., Ltd. (“Wakunaga”), a Japanese pharmaceutical company. I was comfortable at the time that Abbott would not have in-licensed ABT-492 from Wakunaga if Abbott did not actually believe that ABT-492 had reasonable prospects for success. Additionally, the proposed Agreement with Abbott provided that John Hancock would receive a replacement compound if the first of ABT-510 and ABT-492 did not progress in clinical trials. Accordingly, I did not see a need to reengage Dr. Klotz to evaluate that compound.

62. After reviewing the information regarding ABT-510 and ABT-492, and confirming that the inclusion of those compounds, in addition to certain other changes in John Hancock’s proposed payments and the milestone and royalty payments proposed to be made by Abbott, in John Hancock’s Monte Carlo simulation model resulted in a sufficiently improved rate of return and reduced level of risk, John Hancock accepted Abbott’s proposal to replace ABT-980 in or about early February 2001.

63. At the same time, I recall expressing concern to Abbott that, with the addition of ABT-510, John Hancock’s planned “diverse” basket of compounds was becoming overly-concentrated on potential cancer therapies. As a solution, Abbott proposed, and I agreed, to remove Abbott’s pre-clinical “Urokinase Program” from the proposed basket and replace it with Abbott’s pre-clinical “Erectile Dysfunction” or “ED Program.” Abbott further agreed that, if the initial compound that emerged from its ED Program failed to proceed past Phase I, Abbott would replace that failed compound with the next Phase I compound to emerge from its

ED Program. Abbott's agreement on this point, plus my own review of the available information, gave me sufficient confidence to add the pre-clinical ED Program to the basket of compounds in place of the Urokinase Program without additional input from Dr. Klotz.

64. Abbott and John Hancock thereafter continued to modify and refine the terms of their proposed Research Funding Agreement in various ways, but the group of nine "Program Compounds" encompassed by that Agreement remained unaltered through the Agreement's execution on March 13, 2001.

The Final Agreement

65. The final Agreement between John Hancock and Abbott was executed by me and Dr. Jeffrey Leiden, then Executive Vice President of Abbott's Pharmaceuticals Division and its Chief Scientific Officer, on March 13, 2001. A true and accurate copy of the executed Agreement, dated March 13, 2001, is attached hereto as Ex. 32.

66. On March 12, 2001 (*i.e.*, the day before the Research Funding Agreement was executed), I received another e-mail message from Mr. Deemer in which he expressly assured me that Dr. John Leonard, Abbott's Vice President of Development, had "looked at all of the documents one last time in preparation for execution" and noted just "one oversight on one of the Programs"; a delay in the commencement of Abbott's Phase I study of ABT-518, which "was to have started on December 2000 (4Q2000) but in fact did not start until earlier this month" (*i.e.*, March 2001). Mr. Deemer further informed me that, although the delay in the commencement of Abbott's Phase I trial of ABT-518 "pushed the timeline [for that compound] back by a quarter throughout," Abbott's estimated "launch date" for ABT-518 was "not affected and is actually planned one quarter earlier." He attributed Abbott's delay in "starting some of these earlier compound studies" to delays in "completing this financing and hence the

reason this one got pushed back a little.” A true and accurate copy of Mr. Deemer’s e-mail message to me, dated March 12, 2001, is attached hereto as PLs’ R.

67. I understood, at the time that I received Mr. Deemer’s e-mail message on March 12, 2001, that he was updating me on the condition of, and the prospects for, the Program Compounds pursuant to Abbott’s obligations under Section 12.2(m) of the final Agreement, in which Abbott expressly represented and warranted to Hancock that,

[w]ith respect to each Program Compound, since the date of its respective Compound Report, to the knowledge of Abbott, no condition, circumstance or fact has arisen (other than generally available information concerning the pharmaceutical industry in general) nor has Abbott made any change in the conduct of the Research Program which, individually or in the aggregate, has resulted in, or could reasonably be expect[ed] to result in, a material adverse effect on the prospects or condition (including safety, efficacy, scientific viability or commercial [viability]) of such Program Compounds.

68. The news that Abbott’s Phase I trial of ABT-518 had been delayed a few months did not concern me in any material way, particularly in light of Mr. Deemer’s simultaneous representation that Abbott actually intended to commercialize that compound three months earlier than previously disclosed. Of much greater significance to me was the fact that neither Mr. Deemer, nor Dr. Leonard identified, on March 12, 2001, any other material change in the condition of, prospects for, or Abbott’s plans for, any of the Program Compounds. I regarded their silence in this regard as confirmation by Abbott, pursuant to the terms of the Agreement, that no other such change had taken place, and that there was no reason for John Hancock not to proceed with the Agreement.

69. From the time that I received Mr. Deemer’s e-mail message on March 12, 2001, up until the execution of the Agreement the following day, no additional changes,

concerns, discrepancies or errors in the documentation regarding the various Program Compounds were disclosed to me or, based on my observations, to anyone else at John Hancock by Abbott.

70. The terms of the final Agreement that was signed on March 13, 2001 call for John Hancock to invest up to \$214 million over four years in the development of nine Program Compounds including, but not limited to, ABT-518, ABT-594 and ABT-773.

71. Under the terms of the Agreement, John Hancock's ability to earn a return on its investment in the Program Compounds depends on the commercial success of those compounds. If some or all of the compounds fail or otherwise are unsuccessful, Hancock's financial return is reduced accordingly.

72. Similarly, because John Hancock only shares in the revenues, if any, generated by the Program Compounds for a set number of years, Hancock stands to gain more if the Program Compounds are developed quickly.

73. The final Descriptive Memoranda (also referred to in the Agreement as "Compound Reports") were attached to, and incorporated in, the Agreement as collective Exhibit 12.2(i). Abbott's purported spending plans as of the date of the Agreement were contained in its first ARP, which was attached to, and incorporated in, the Agreement as Exhibit 1.6.

74. Abbott expressly represented and warranted both the completeness and the accuracy of the information contained in its Descriptive Memoranda and in its first ARP in Article 12 of the Agreement. More specifically, Abbott represented and warranted to John Hancock in Section 12.2(i) that,

[n]either this Agreement nor any Exhibit to this Agreement (including the compound reports attached as Exhibit 12.2(i) hereto (the "Compound Reports")) contains any untrue statement of material fact or omits to state any material fact necessary to make the statements contained therein not misleading. There is no fact known to Abbott (other than generally available information concerning the pharmaceutical industry in general) as of the date of this Agreement that has not been disclosed in this Agreement or any Exhibit to this Agreement which has resulted in, or could reasonably be expected to result in, a material adverse effect on the prospects or condition (including safety, efficacy, scientific viability or commercial [viability]) of the Research Program or any of the Program Compounds.

75. I and, based on my observations, others at John Hancock actually relied upon various express representations made by Abbott in the Agreement, including the representations contained in Sections 12.2(i) and 12.2(m), in the Descriptive Memoranda, and in Abbott's first ARP, in deciding to enter into the Agreement on March 13, 2001 on the terms stated.

76. I regarded, and continue to regard, the representations made by Abbott in Sections 12.2(i) and 12.2(m) of the Agreement, in the Descriptive Memoranda, and in Abbott's first ARP, among others, as material to John Hancock's decision to enter into the Agreement on March 13, 2001 on the terms stated. I would not have recommended that John Hancock enter into the Agreement if Abbott had not agreed to provide Hancock with those representations and warranties.

*Abbott's Misrepresentations and Fraud Regarding the
Actual Status and Prospects of the Program Compounds as of the Date of the Agreement*

77. Since I executed the Research Funding Agreement on John Hancock's behalf on March 13, 2001, I have come to learn that the actual status and prospects of at least three of the Program Compounds, ABT-518, ABT-594 and ABT-773, were materially different from what Abbott represented to Hancock in that Agreement. I also have come to learn that

Abbott's actual plans for at least two of the Program Compounds, ABT-518 and ABT-594, as of March 13, 2001, were materially different from what Abbott represented to John Hancock in the Agreement. The true facts, as I now understand them, include the following.

ABT-518

78. Over the approximately ten months of active contract negotiations leading up to the execution of the Research Funding Agreement, Abbott supplied me and others at John Hancock with three versions of its Descriptive Memorandum for ABT-518 and/or Abbott's "MMPI Program": an initial draft dated May 31, 2000; and updated draft dated November 1, 2000; and the final version dated February 2001. True and accurate copies of Abbott's draft Descriptive Memoranda for ABT-518 are attached hereto as Ex. 1 and 2. Abbott's final Descriptive Memorandum for ABT-518 forms a part of collective Exhibit 12.2(i) to the Agreement, which is attached hereto as Ex. 32.

79. Each version of Abbott's Descriptive Memorandum for ABT-518 states, among other things, that:

- (a) "Abbott's Matrix Metalloproteinase Inhibitor (MMPI) program represents a novel therapeutic class, with the potential to alter the way cancer is treated by preventing or modifying disease progression and/or metastases";
- (b) "The MMPI selectivity profile exhibited by ABT-518 distinguishes it from competitor's compounds"; and
- (c) "ABT-518 is therefore a compelling development candidate with the potential to demonstrate antitumor effects superior to the [other] MMPI inhibitors currently undergoing clinical trials." Abbott further

represented that “Phase I clinical trials” of ABT-518 by Abbott “began March 2001,” and that “[c]linical studies across a wide range of solid tumors will be initiated...”

80. The various versions of Abbott’s Descriptive Memorandum for ABT-518 also consistently identify other “MMPIs in Clinical Development for Cancer” as including “Marimistat” [*sic*], which reportedly was being developed by British Biotechnology and Schering Plough, and “Prinomastat,” which reportedly was being developed by a combination of Agouron Pharmaceuticals, Warner Lambert and Pfizer.

81. With respect to these competing MMPI compounds, each version of Abbott’s Descriptive Memorandum states that,

[a]lthough Abbott’s timing to market is not optimal, the shortcomings of the competitive products provide an opportunity for a compound with an improved SE or efficacy profile. Current animal models seem to predict Abbott’s compound [i.e., ABT-518] is superior to those currently in clinical trials, and has the potential to be best in class.

82. Prior to the execution of the Agreement, Abbott never wavered in its representations to me and to others at John Hancock that Abbott considered ABT-518 to be a “compelling development candidate” that had “the potential to be best in class” among a “novel therapeutic class” of similar compounds being developed by a range of pharmaceutical companies.

83. Since the execution of the Research Funding Agreement, I have learned that Abbott’s express representation in the Agreement that Abbott believed ABT-518 to be a “compelling development candidate” as of March 13, 2001, as well as various other representations that Abbott made to Hancock in the Agreement regarding the purported

prospects and condition of ABT-518, were materially false and/or incomplete. Material facts that Abbott either misrepresented or failed to disclose to me or to others at John Hancock include the following:

- (a) Contrary to the representations made by Abbott in its Descriptive Memorandum for ABT-518, Abbott knew before the Agreement was signed that other pharmaceutical companies had dramatically curtailed or discontinued their own MMPI programs. Members of Abbott's management were aware no later than February 2001 that Agouron Pharmaceuticals and Pfizer had announced the prior summer that they were "stopping Phase III trials of Prinomastat in advanced prostate [cancer] and NSCLC [non-small cell lung cancer] because 'primary efficacy objectives were not met,'" and that "Marimastat development was discontinued" by British Biotech on February 15, 2001; (*See* PLs' I attached);
- (b) Less than one week prior to the execution of the Agreement, the senior management of Abbott's Pharmaceuticals Division -- led by Dr. Leiden and including Dr. Leonard -- reviewed ABT-518's current status and prospects as part of the comprehensive Initial Portfolio Prioritization Review that they conducted on March 7-9, 2001. Questions were raised about ABT-518 during the course of the review in light of the information that several competitor MMPIs already had been discontinued; (*See* PLs' M, N, BL, EZ attached);
- (c) Shortly after the presentation and discussion concerning ABT-518, Dr. Leiden, in his capacity as Executive Vice President of Abbott's Pharmaceuticals Division and its Chief Scientific Officer, ordered an immediate halt to all

expenditures on the development of ABT-518 due to his concerns about the low prospects of success for that compound; (*See* PLs' X, BL, FH, PH, PJ, PT attached);

- (d) Consistent with the decision made at Abbott's Initial Portfolio Prioritization Review in early March 2001, Abbott personnel working on ABT-518 were instructed by their superiors on Sunday, March 11, 2001 (*i.e.*, two days before the Agreement was executed), to "stop all development activities immediately." I understand that Dr. Azmi Nabulsi, an Abbott employee who was working on the Phase I study of ABT-518 that Abbott recently had commenced in the Netherlands, notified his counterpart in Europe the same day that "we are not proceeding with the trial as a result of the [ABT-518] projects re-prioritization following the acquisition of Knoll"; (*See* PLs' X, BL, PJ attached);
- (e) As a consequence of Abbott's order to stop all development activities on ABT-518 immediately because of the low prospects of success for that compound, further enrollment in the Phase I trial of ABT-518 was halted on or about March 12, 2001 (*i.e.*, the day before the Agreement was executed); (*See* PLs' T, X, Z, BL attached);
- (f) When Mr. Deemer learned, just before the Agreement was signed, that Abbott's senior management had decided to halt further development of ABT-518, he contacted Dr. Leonard to remind him that ABT-518 was one of the Program Compounds in the planned John Hancock portfolio of compounds. Dr. Leonard, in turn, promptly spoke with Dr. Leiden, reminded him of the

impending Agreement with John Hancock, and suggested that Abbott proceed with the development of ABT-518; (*See* PLs' AB attached); and

- (g) On March 13, 2001 (*i.e.*, the day the Agreement was executed), Dr. Leiden directed Abbott personnel to recommence the Phase I trial of ABT-518 and signed the Agreement on Abbott's behalf. (*See* Ex. 32 and PLs' V, X, BL attached).

84. I further understand that the Phase I trial of ABT-518 did not immediately recommence on March 13, 2001. It took Abbott personnel and the clinicians at the trial sites more than another week to resume patient enrollment in the trial. (*See* PLs' AC attached). I also understand that certain other development work on ABT-518, including various toxicology tests and analyses, never was resumed by Abbott after being halted, per Dr. Leiden's order, on or about March 12, 2001. (*See* PLs' AP attached).

85. None of the facts set forth in Paragraph 83 of this Affidavit was disclosed to me or, based on my observations, to others at John Hancock either in the Research Funding Agreement or otherwise before I executed that Agreement on Hancock's behalf.

86. The true prospects and condition of ABT-518 as of March 13, 2001 was information material to my decision and, based on my observations, the decision of others at John Hancock to recommend and to enter into the Agreement with Abbott on the terms stated therein.

87. Had Abbott informed me or others at John Hancock of the true prospects and condition of ABT-518 as of March 13, 2001, as set forth, *inter alia*, in Paragraph 83 of this Affidavit, that information would have significantly and adversely altered the economics and attractiveness of the proposed funding deal from my perspective. It would have reduced John

Hancock's expected return and increased Hancock's risk of total loss. I believe that, in such circumstances, I would not have recommended that John Hancock enter into the Agreement in its present form, and it is quite possible that I ultimately would not have recommended that Hancock enter into any funding agreement with Abbott at all.

88. For example, if Mr. Deemer or Dr. Leonard had notified me on or prior to March 13, 2001, that Dr. Leiden, in his capacity as Executive Vice President of Abbott's Pharmaceuticals Division and its Chief Scientific Officer, had ordered an immediate halt to all expenditures on the development of ABT-518 *just days before* due to Dr. Leiden's concerns about the low prospects of success for that compound, I am confident that I would not have signed the Agreement in its present form, which includes ABT-518, on that date. John Hancock had no interest in investing millions of dollars in compounds that already had been discontinued by Abbott, or that Abbott knew or had reason to believe would be discontinued shortly.

89. Had Abbott been more forthcoming regarding the actual condition of, and prospects for, ABT-518 on or prior to March 13, 2001, I believe that, at a minimum, the execution of the Research Funding Agreement would have been delayed for a period of weeks or months to allow the parties to renegotiate the terms of the Agreement to compensate John Hancock for the apparent or impending loss of ABT-518 from Hancock's portfolio of compounds.

90. If I had ceased to recommend that John Hancock enter into the proposed Agreement with Abbott at any time on or prior to March 13, 2001, on account of any actual or perceived problems concerning the condition of, or prospects for, ABT-518, I am confident that that Agreement would not have gone forward.

91. Abbott did not notify me or, based on my observations, anyone else at John Hancock of its final decision to terminate ABT-518 until September 20, 2001, at which time Abbott stated only that it had “refocused its efforts in cancer discovery and, as a result, has made the decision to terminate the MMPI Program, which includes Program Compound ABT-518.” Abbott provided me with no additional information regarding the basis for, or the history of, its decision to terminate ABT-518 at that time. A true and accurate copy of Daphne Pals, Esq.’s letter to me notifying me of Abbott’s final decision to terminate ABT-518, dated September 20, 2001, is attached hereto as Ex. 13.

ABT-594

92. Over the approximately ten months of active contract negotiations leading up to the execution of the Research Funding Agreement, Abbott supplied me and others at John Hancock with three versions of its Descriptive Memorandum for ABT-594: a initial draft dated April 2000; an updated draft dated November 2000; and a final draft, dated February 2001. True and accurate copies of the draft ABT-594 Descriptive Memorandum, dated April 2000, and the draft ABT-594 Descriptive Memorandum, dated November 2000, are attached hereto as PLs’ CC and DL. Abbott’s final Descriptive Memorandum for ABT-594 forms a part of collective Exhibit 12.2(i) to the Agreement, which is attached hereto as Ex. 32.

93. With minor variations, each version of Abbott’s Descriptive Memorandum for ABT-594 describes that compound, among other things, as follows:

- (a) “ABT-594 is a non-opioid, non-[steroidal anti-inflammatory drug] analgesic ... that is 30 to 100-fold more potent and equally efficacious to morphine in several well-characterized animal models of pain”;

- (b) Abbott's "initial targeting indication [for ABT-594] is symptomatic treatment of diabetic neuropathic pain";
- (c) "[t]he preclinical side effect and dependency liability profile of ABT-594 is superior to that of morphine";
- (d) ABT-594 was "expected to be the first neuronal nicotinic receptor agonist to receive an indication for pain" and "has a novel mechanism of action and a potentially broad coverage of chronic pain conditions" in addition to "an opioid-like, efficacy without tolerance, dependence or abuse potential, while having equivalent/superior efficacy to other drugs used to treat neuropathic pain";
- (e) a "phase IIb study for neuropathic pain at higher, titrated doses of ABT-594 began in April 2000 and ends in June 2001" with a "total of 320 patients anticipated to be included in the study";
- (f) and a "[New Drug Application] filing" with the FDA for ABT-594 was "expected in 3Q2003."

94. Abbott simultaneously represented to me and to others at John Hancock in its first ARP that Abbott's "2001 Current Projection (Plan)" for spending on ABT-594 as of the date of the Agreement was "35.0" million dollars, including over \$11.5 million for new Phase II and Phase III studies of the compound that Abbott purportedly planned to commence in Calendar Year 2001.

95. Prior to the execution of the Agreement, Abbott never wavered in its representations to me and to others at John Hancock that ABT-594 had "an opioid-like efficacy without tolerance, dependence or abuse potential," and that Abbott expected ABT-594 "to be the first neuronal nicotinic receptor agonist to receive an indication for pain."

96. Since the execution of the Research Funding Agreement, I have learned that Abbott's express representation in the Agreement that Abbott "expected" ABT-594 "to be the first neuronal nicotinic receptor agonist to receive an indication for pain" as of March 13, 2001, as well as various other representations that Abbott made to Hancock in the Agreement regarding the prospects and condition of ABT-594 and Abbott's expected spending on that compound, were materially false and/or incomplete. Material facts that Abbott either misrepresented or failed to disclose to me and to others at John Hancock include the following:

- (a) Abbott's Phase IIb trial of ABT-594 for the treatment of diabetic neuropathic pain (known within Abbott as trial "M99-114") commenced in April 2000. The Phase IIb trial was designed to include 320 "subjects" or patients in a "double-blinded" format in order to achieve what Abbott perceived would be a statistically significant result. Almost immediately, Abbott's Phase IIb trial encountered problems with "premature terminations" (*i.e.*, subjects dropping out of the trial early) due primarily to "adverse events" ("AEs") or side effects among trial subjects including moderate-to-severe nausea, emesis (*i.e.*, vomiting) and dizziness; (*See* Ex. 16, 18 and PLs' CF, BY attached);
- (b) By June 2000, Abbott's ABT-594 Product Development Team already was reviewing the available "strategic options" to address the slow enrollment of subjects in the trial. The premature termination and enrollment problems did not improve, however. As of July 7, 2000, of the 78 subjects who had entered Abbott's Phase IIb study of ABT-594, "at least" 31 had prematurely terminated their involvement in the study due to adverse events; (*See* PLs' CE, CJ, CK attached);

- (c) By August 2000, there was “much concern with the drop out rate” in the Phase IIb trial among members of Abbott’s ABT-594 Product Development Team; (*See* PLs’ CN attached);
- (d) Abbott continued to try various measures in the summer and fall of 2000 to address the premature termination and enrollment problems that it was encountering in its Phase IIb trial of ABT-594, including sending written surveys to the various clinical test sites to “examine AEs (nausea, vomiting, and dizziness),” and extending the enrollment deadline for the trial from September 22, 2000, to March 2, 2001. I understand that Abbott even investigated the possible use of one or more outside patient recruitment firms to assist in identifying and enrolling more subjects in the study. The patient recruitment firms that Abbott solicited (but not John Hancock) were informed, *inter alia*, that the Phase IIb study had a “[h]igh study dropout rate of 34% primarily due to side effects of the investigational drug”; (*See* PLs’ CM, CR, CW, CZ attached);
- (e) By the fall of 2000, members of Abbott’s senior management regarded ABT-594 as having “questionable commercial viability”; (*See* PLs’ CU, DT, PI attached);
- (f) In mid-to-late 2000, Abbott employees with responsibility for supervising the Phase IIb trial of ABT-594 reviewed the preliminary, blinded trial data and concluded that the episodes of nausea and vomiting observed in the trial probably were dose-related. I understand that they considered, but ultimately rejected, revising the trial while it was underway to eliminate the highest dosage

(i.e., 300 microgram) cohort in an effort to reduce the observed rate of nausea and vomiting; (See PLs' CJ, CK attached);

- (g) In early December 2000, Abbott's management decided not to retain a patient recruitment firm for its Phase IIb study of ABT-594, concluding that doing so was not a "viable option at this time"; (See PLs' DJ, DV attached);
- (h) Rather than continue to try to bolster patient enrollment in its Phase IIb trial of ABT-594, Abbott decided in December 2000 to prematurely terminate that trial as of January 5, 2001, a date that Abbott recognized was "2 months ahead of [its] most recent estimate of March 5, 2001" and would result in "less than [Abbott's] original target of 320 patients"; (See Ex. 20 and PLs' FZ attached);
- (i) Enrollment in Abbott's Phase IIb study of ABT-594 actually was stopped on January 5, 2001, at 266 subjects; (See PLs' FZ attached);
- (j) Abbott understood as of December 2000 that prematurely terminating its Phase IIb study of ABT-594 at less than 320 subjects would undermine the statistical validity of that study and render it effectively useless for advancing the further development of ABT-594; (See PLs' CW, HK attached);
- (k) Abbott made the decision in early December 2000 to prematurely terminate its Phase IIb trial of ABT-594 based, in significant part, on the belief of Abbott personnel that the final results of that trial were likely to demonstrate that ABT-594 was not a viable commercial product;
- (l) Abbott made what it described internally as "significant changes" in its developmental strategy for ABT-594 at or around the time that Abbott decided to prematurely terminate its Phase IIb trial of that compound. I understand that

those significant changes included Abbott's decision in late 2000 to explore a potential co-development partnership for ABT-594 with other pharmaceutical companies; (*See* Ex. 24 and PLs' FZ attached);

- (m) Abbott personnel were concerned, however, about the potential impact of disclosing what was described internally at Abbott as ABT-594's "nausea and vomiting issue" to possible co-development partners; (*See* PLs' DM attached);
- (n) In the end, none of the pharmaceutical companies that Abbott approached in late 2000 or early 2001 concerning ABT-594 was willing to enter into a co-development agreement for that compound;
- (o) At or around the same time that Abbott made significant changes in its developmental strategy for ABT-594 and began searching for a co-development partner for that compound, Abbott significantly reduced its planned spending on ABT-594 for Calendar Year 2001. Although Abbott continued to represent to me and to others at John Hancock in drafts and in the final version of its first ARP that it expected spending "35.0" million dollars on the development of ABT-594 in 2001, Abbott's actual planned spending on ABT-594 in 2001 had dropped, as of early March 2001, to approximately \$9.3 million, a reduction of more than 73 percent; (*See* Ex. 32 and PLs' LW, MB, RX attached);
- (p) Abbott's reduced spending for 2001 included enough funds to complete a "Go/No Go" decision regarding ABT-594 following the prematurely terminated Phase IIb trial, but did not include any funding for the previously planned additional Phase II or Phase III trials of that compound, which were described in

Abbott's internal 2001 Plan Final Reference Package as having been "Delayed";
(See PLs' LW, MB attached);

- (q) Representatives of Abbott's ABT-594 Product Development Team made a presentation concerning ABT-594 to members of Abbott's senior management (including Dr. Leiden) on February 2, 2001. I understand that information concerning the prematurely terminated Phase IIb trial was included in the presentation. The presentation also included information about potential NNR "back-up" or "follow-on" compounds to ABT-594. I further understand that, at the conclusion of the presentation, Abbott's management recommended that Abbott personnel develop a "comprehensive strategy to address tolerability issues related to NNRs for pain, including ABT-594 and follow-ons"; (See PLs' EL, EN, EO attached);
- (r) By February or early March 2001, Abbott scientific personnel who were charged with discovering and developing new NNR compounds had concluded that "ABT-594 ... is an imperfect drug" due, in large part, to the "key adverse events of emesis, nausea, and dizziness that have consistently been observed during clinical evaluation of ABT-594"; (See PLs' EV, ES attached);
- (s) Members of Abbott's senior management, including Drs. Leiden and Leonard, reviewed ABT-594 again in the course of Abbott's Initial Portfolio Prioritization Review on March 7-9, 2001. I understand that preliminary data from the recently discontinued Phase IIb trial of ABT-594 was discussed during the Initial Portfolio Prioritization Review, and concerns were expressed about the data; (See PLs' FB, EZ attached); and

- (t) As part of, or shortly after, the Initial Portfolio Prioritization Review, members of Abbott's senior management, again including Dr. Leiden, met in executive session and discussed what they thought would be the likely outcome of the Phase IIb trial of ABT-594 and, ultimately, Abbott's development program for that compound. I understand that Abbott's senior management surmised that the Phase IIb trial outcome would be negative, with the result that they likely would terminate ABT-594. (*See* PLs' FH attached).

97. I understand that Abbott terminated the development of ABT-594 not long after the results of the Phase IIb neuropathic pain trial were officially unblinded in April 2001. I further understand that those results confirmed that each of the three dosages of ABT-594 tested in the study "Were Associated with a Dose Dependent Increase in Adverse Events, Especially Nausea, Vomiting and Dizziness," and that the resultant "Unfavorable Side Effect Profile" was sufficient to terminate the compound.

98. None of the facts set forth in Paragraph 96 of this Affidavit was disclosed to me or, based on my observations, to others at John Hancock either in the Research Funding Agreement or otherwise before I executed that Agreement on Hancock's behalf.

99. The true prospects and condition of ABT-594 as of March 13, 2001, as well as Abbott's expected spending on that compound, was information material to my decision and, based on my observations, the decision of others at John Hancock to recommend and to enter into the Agreement with Abbott on the terms stated therein.

100. Had Abbott informed me or others at John Hancock of the true prospects and condition of ABT-594 as of March 13, 2001, as set forth, *inter alia*, in Paragraph 96 of this Affidavit, that information would have significantly and adversely altered the economics and

attractiveness of the proposed funding deal from John Hancock's perspective. It would have dramatically reduced John Hancock's expected return and dramatically increased Hancock's risk of total loss. I believe that, in such circumstances, I would not have recommended entering into that Agreement in its present form or, more likely, that I ultimately would not have recommended that John Hancock enter into any funding agreement with Abbott at all.

101. For example, if Mr. Deemer or Dr. Leonard had notified me on or prior to March 13, 2001, that Abbott had prematurely terminated its Phase IIb trial of ABT-594 in early January 2001 at less than its target of 320 patients due to a large number of adverse events involving, among other things, moderate-to-severe nausea and vomiting, that Abbott had decided to reduce its own planned spending on that compound in Calendar Year 2001 by over seventy percent, or that Abbott's senior management had determined *just days before* that Abbott probably would terminate the development of ABT-594 when the final results of that Phase IIb trial were unblinded, I am confident that I would not have signed the present Agreement, which includes ABT-594, on that date. As previously stated, John Hancock had no interest in investing millions of dollars in compounds that already had been discontinued by Abbott, or that Abbott knew or had reason to believe would be discontinued shortly.

102. If I had ceased to recommend that John Hancock enter into the proposed Agreement with Abbott at any time on or prior to March 13, 2001, on account of any actual or perceived problems concerning the condition of, or prospects for, ABT-594, I am confident that that Agreement would not have gone forward.

103. Abbott did not notify me or, based on my observations, anyone else at John Hancock of its decision to terminate ABT-594 until November 16, 2001, at which time Abbott stated only that it had "decided to terminate further development of ABT-594 (a drug for the

treatment of neuropathic pain).” Abbott provided me with no additional information regarding the basis for, or the history of, its decision to terminate ABT-594 at that time. A true and accurate copy of Daphne Pals, Esq.’s letter to me notifying me of Abbott’s final decision to terminate ABT-594 (with the handwritten notes of Abbott personnel), dated November 16, 2001, is attached hereto as PLs’ GL.

ABT-773

104. Over the approximately ten months of active contract negotiations leading up to the execution of the Research Funding Agreement, Abbott supplied me and others at John Hancock with three versions of its Descriptive Memorandum for ABT-773: an initial draft dated June 5, 2000; an updated draft dated November 1, 2000; and the final version, dated February 2001. True and accurate copies of the draft ABT-773 Descriptive Memorandum, dated June 5, 2000, and the draft ABT-773 Descriptive Memorandum, dated November 1, 2000, are attached hereto as PLs’ HX and IA. Abbott’s final Descriptive Memorandum for ABT-773 forms a part of collective Exhibit 12.2(i) to the Agreement, which is attached hereto as Ex. 32.

105. Each version of Abbott’s Descriptive Memoranda for ABT-773 states, among other things, that:

- (a) “Product features such as high efficacy, activity against resistant strains of bacteria and convenience should enable [ABT-773] to compete against both Zithromax and newer agents such as quinolones”;
- (b) “[d]osing is expected to be once-a-day” and a “5-day convenience pack at a competitive price will help maximize sales”; and

- (c) “[t]he likely profile of ABT-773 justifies further development [because] ABT-773 pertains to new class of antibiotics, good activity against resistant Gram+ organisms, particularly macrolide-resistant *S. pneumoniae*, convenience, safety and tolerability profile competitive with [Zithromax], and oral suspension and I.V. forms enabling penetration into pediatrics and hospital segments.”

106. I understood as of 2000-2001 that Zithromax is a competing macrolide-based antibiotic that already was commercially available. I further understood, based on Abbott’s statements, that Abbott believed Zithromax’s tolerability had “redefined expectations for tolerability of new agents” and had “moved the market toward short course therapies dosed once daily.”

107. I understood as of 2000-2001 that quinolones are yet another type of antibiotic with which ABT-773 potentially would compete.

108. Prior to the execution of the Agreement, Abbott never wavered in its representations to me and to others at John Hancock that ABT-773 was expected to have “once-a-day” or “QD” dosing and a “[c]onvenience, safety and tolerability profile competitive” with Zithromax, and that Abbott was developing “[o]ral suspension and I.V. forms” of ABT-773 that would “enabl[e] penetration into pediatrics and hospital segments.”

109. Since the execution of the Research Funding Agreement, I have learned that Abbott’s express representation in the Agreement that Abbott “expected” ABT-773 to have “once-a-day” dosing and a “[c]onvenience, safety and tolerability profile competitive” with Zithromax, as well as various other representations that Abbott made to Hancock in the Agreement regarding the prospects and condition of ABT-773, were materially false and/or

incomplete. Material facts that Abbott either misrepresented or failed to disclose to me and to others at John Hancock include the following:

- (a) Although not referenced anywhere in the Agreement, Abbott had significant, unresolved issues concerning the safety of ABT-773 as of March 2001, particularly with respect to the potential for abnormal heartbeat prolongation (also known as “QT” or “QTc” prolongation) and chemical-driven liver damage (also known as “hepatotoxicity,” “hepatotoxicity,” “liver toxicity” or simply “liver tox”) among clinical trial subjects who took the compound. I understand that Abbott already had seen some evidence of possible liver toxicity during preclinical testing and among Japanese patients in an early study of ABT-773 conducted in Hawaii. Moreover, I understand that, “despite significant issues with the quality of the QT data collection to date,” senior Abbott personnel working on the development of ABT-773 internally recognized by early 2001 that a “QT signal has emerged from both the pre-clinical and clinical programs” sufficient “to establish that there probably is an issue....”; (*See* PL’s IN, IO, IP, IW attached);
- (b) Abbott personnel had discussions concerning ABT-773 with representatives of the FDA in late 2000 in which the FDA described “hepatotoxicity and QT changes” as the “two primary toxicities they are worried about with macrolides and ketolides,” and asked Abbott to undertake additional dog toxicology testing of ABT-773 focused specifically on those issues. I understand that, by February 2001, Abbott internally was describing “QTc Issues” and “Liver Toxicity Issues” as “Key Issues Facing the ABT-773 development program.” I further

understand that both of these “Key Issues” remained unresolved when Abbott and John Hancock entered into the Agreement just one month later; (*See* PLs’ IB, IC, ID, IE, IF attached);

- (c) Abbott recognized well before the Agreement with John Hancock was signed in March 2001 that a “once-a-day formulation [of ABT-773] may not be possible based on the short half-life of the drug and the apparent short absorption window in the GI tract.” I understand that, in June 2000, Abbott internal documents described “[u]ncertainty in ABT-773 convenience profile *i.e.* potential for [twice-a-day] dosing” as one of the “Key Commercial Issues” facing ABT-773; (*See* PLs’ HS, HW attached);
- (d) Although Abbott represented to John Hancock in the Agreement that the dosing of ABT-773 was “expected to be once-a-day,” Abbott had concluded one month earlier that 300 mg, once-a-day dosing of ABT-773 “was not viable” for any indication “due to high levels of diarrhea (10-20%) and taste perversion (10-20%),” and still needed data from an ongoing Phase III trial before it could determine whether 150 mg, once-a-day dosing might be viable for two of the four target indications; CAP (community acquired pneumonia) and sinusitis (chronic sinus infection). I understand that Abbott simultaneously recognized that the “[a]bsence of consistent QD dosing for all indications” presented “a significant commercial hurdle” for ABT-773 in the United States; (*See* Ex. 32 and PLs’ IN, IP attached);
- (e) Abbott knew, prior to March 2001, that the development of a pediatric oral-suspension formulation of ABT-773 would be “very difficult” because taste tests

showed the compound to be “5 to 7 times more bitter than clarithromycin,” another antibiotic that Abbott already marketed under the trade name Biaxin®. I understand that Abbott further knew that its inability to develop a pediatric formulation of ABT-773 could pose a significant regulatory hurdle for that compound in the United States because of FDA rules; (*See* PLs’ IN, IO, IP, IQ attached); and

- (f) Notwithstanding, Abbott’s entire pediatric oral suspension program for ABT-773 was “on hold” and unfunded as of early 2001. (*See* PLs’ IO, IQ attached).

110. I understand that the material information concerning the prospects and condition of ABT-773 that Abbott misrepresented or failed to disclose to me and to others at John Hancock in the Agreement played an important role in the subsequent decision of Abbott’s Pharmaceutical Executive Committee (“PEC”) to recommend in early December 2001, less than nine months after the Agreement was executed, that Abbott’s entire ABT-773 development project “be put on hold,” and that Abbott make efforts to “aggressively pursue out-licensing or selling the compound.” (*See* Ex. 28 attached).

111. None of the facts set forth in Paragraph 109 of this Affidavit was disclosed to me or, based on my observations, to others at John Hancock either in the Research Funding Agreement or otherwise before I executed that Agreement on Hancock’s behalf.

112. The true prospects and condition of ABT-773 as of March 13, 2001 was information material to my decision and, based on my observations, the decision of others at John Hancock to recommend and to enter into the Agreement with Abbott on the terms stated therein.

113. Had Abbott informed me or others at John Hancock of the true prospects and condition of ABT-773 as of March 13, 2001, as set forth, *inter alia*, in Paragraph 109 of this Affidavit, that information would have significantly and adversely altered the economics and attractiveness of the proposed funding deal from John Hancock's perspective. It would have dramatically reduced John Hancock's expected return and dramatically increased Hancock's risk of total loss. It also would have indicated that there was a significant risk that ABT-773, even if eventually successful, would be substantially delayed and, therefore, less valuable to John Hancock. I believe that, in such circumstances, I would not have recommended entering into that Agreement in its present form or, more likely, that I ultimately would not have recommended that John Hancock enter into any funding agreement with Abbott at all.

114. For example, if Mr. Deemer or Dr. Leonard had notified me on or prior to March 13, 2001, that Abbott had significant, unresolved issues concerning the safety of ABT-773 as of March 2001 (particularly with respect to the potential for abnormal heartbeat prolongation and liver toxicity among clinical trial subjects who took the compound), that the FDA was sufficiently concerned about these issues to ask Abbott to perform additional animal toxicity testing of ABT-773, or that Abbott already had determined that once-a-day dosing of ABT-773 might not be viable for some or all of its intended indications, I am confident that I would not have signed the present Agreement, which includes ABT-773, on that date. As previously stated, John Hancock had no interest in investing millions of dollars in compounds that already had been discontinued by Abbott, or that Abbott knew or had reason to believe would be discontinued shortly.

115. If I had ceased to recommend that John Hancock enter into the proposed Agreement with Abbott at any time on or prior to March 13, 2001, on account of any actual or

perceived problems concerning the condition of, or prospects for, ABT-773, I am confident that that Agreement would not have gone forward.

116. On or about December 20, 2001, I had a conference call with Thomas Lyons, the Controller of Abbott's Global Pharmaceutical Research and Development Division, and I believe others at Abbott for the purpose of obtaining an update regarding the status of the various Program Compounds. At no time during that conference call (or thereafter) did Mr. Lyons or any other Abbott representative disclose to me that Abbott's PEC had voted, less than two weeks earlier, to recommend that Abbott's entire ABT-773 development project "be put on hold," and that Abbott make efforts to "aggressively pursue out-licensing or selling the compound."

117. On or about December 26, 2001, I received a copy of Abbott's 2001 Program Status Report pursuant to Section 2.5 of the Agreement. A true and accurate copy of that Program Status Report with a cover letter from Mr. Lyons, dated December 18, 2001, is attached hereto as PLs' MZ. Nowhere in that 2001 Program Status Report did Abbott disclose to me that Abbott's PEC had voted, less than two weeks earlier, to recommend that Abbott's entire ABT-773 development project "be put on hold," and that Abbott make efforts to "aggressively pursue out-licensing or selling the compound."

118. Abbott never formally notified me or, based on my observations, anyone else at John Hancock of its decision to terminate ABT-773 as Abbott had done in the past with ABT-518 and ABT-594. I believe that I first learned of that decision in the course of a conference call with Abbott personnel in or about July 2002.

*Abbott's Misrepresentations and Fraud
Concerning Its Intended and Reasonably Expected Spending*

119. Section 2.2 of the Agreement requires Abbott, *inter alia*, to provide John Hancock, at least forty-five days (45) prior to the start of each Program Year, with a written ARP that spells out Abbott's expected Research Program expenditures on qualified research and development expenses (defined in Section 1.43 of the Agreement as "Program Related Costs") for that year and for each year remaining in the four-year "Program Term."

120. If Abbott's ARP for any given year did not "reasonably demonstrate [Abbott's] ... intent and reasonable expectation to expend on Program Related Costs during the Program Term an amount in excess of the Aggregate Spending Target" as set forth in the Agreement (*i.e.*, \$614 million), then John Hancock's "obligation to make any remaining Program Payments for any succeeding Program Years" automatically would terminate pursuant to Section 3.4(iv) of the Agreement.

121. At various points in time, Abbott provided me and others at John Hancock with documents that purported to set forth Abbott's "intended and reasonably expected" spending on the Program Compounds, including Abbott's ARPs for the First (2001), Second (2002), Third (2003) and Fourth (2004) Program Years. True and accurate copies of those ARPS are attached hereto as Ex. 32, 34 and PLs' MX, NK, and NO.

122. I and, based on my observations, others at John Hancock actually relied on the "intended and reasonably expected" spending information contained in Abbott's various ARPs for the purpose of administering Hancock's payment obligations under the Agreement. For example, I examined and relied upon Abbott's representations regarding its "intended and reasonably expected" spending on the Program Compounds contained in Abbott's ARP for

2002 in subsequently concluding that John Hancock was obligated to make its Second Program Payment in the amount of \$54 million to Abbott in January 2003.

123. Since the execution of the Research Funding Agreement, I have learned that Abbott misrepresented its “intended and reasonably expected” expenditures on Program Related Costs in ARPs that it provided to me and to others John Hancock, including its ARP for 2002. I understand that the Research Program cost projections that Abbott has provided to John Hancock in its various ARPs reflect Abbott’s “nominal” spending, as opposed to its “expected” spending. I further understand that, at all relevant times, Abbott’s actual “intended and reasonably expected” spending on Program Related Costs was considerably less than the amounts communicated to me and others at John Hancock in Abbott’s various ARPs, including its ARP for 2002.

124. Had Abbott informed me and others of its actual “intended and reasonably expected” spending plans on Program Related Costs in its various ARPs as required under the terms of the Agreement, including in its ARP for 2002, I believe that John Hancock quite possibly would not have been required to make, and I believe Hancock quite possibly would not have made, its Second Program Payment in the amount of \$54,000,000 in January 2003.

*John Hancock's Right to Receive a Partial Refund of Its Program Payments
Based Upon Abbott's Failure to Spend the Entire Aggregate Carryover Amount*

125. In the Research Funding Agreement, Abbott agreed to spend a minimum of \$614 million (the "Aggregate Spending Target") on Program Related Costs over the four-year Program Term.

126. Under Sections 1.18, 1.44 and 1.45 of the Research Funding Agreement, the "Program Term" commenced on the "Execution Date" of the Agreement (*i.e.*, March 13, 2001), and ended four "Program Years" later on December 31, 2004.

127. Section 3.3(b) of the Agreement provides that,

[i]f Abbott does not expend on Program Related Costs the full amount of the Aggregate Spending Target during the Program Term, Abbott will expend the difference between its expenditures for Program Related Costs during the Program Term and the Aggregate Spending Target (the "Aggregate Carryover Amount") on Program Related Costs during the subsequent year commencing immediately after the end of the Program Term. If Abbott does not spend the Aggregate Carryover Amount on Program Related Costs during such subsequent year, Abbott will pay to John Hancock one-third of the Aggregate Carryover Amount that remains unspent by Abbott, within thirty (30) days after the end of such subsequent year.

128. The "subsequent year commencing immediately after the end of the Program Term" was the calendar year ending on December 31, 2005.

129. Section 2.5 of the Agreement further provides, in relevant part, that,

Abbott shall, no later than thirty (30) days before the last day of each Program Year, provide John Hancock with a reasonably detailed report setting forth the status of the Research Program and all Program Related Costs expended by Abbott during such Program Year.

130. At various points in time, Abbott provided me and others at John Hancock, pursuant to Section 2.5 of the Agreement, with documents purporting to be Abbott's "Program

Status Reports” for the various Program Years, including Abbott’s Program Status Reports for the First (2001), Second (2002), Third (2003), Fourth (2004), Fifth (2005), Sixth (2006) and Seventh (2007) Program Years. True and accurate copies of those Program Status Reports are attached hereto as Ex. 43 and PLs’ MZ, NK, NN, OZ, PC, and RU.

131. I understand from the various Program Status Reports that Abbott provided to me and others at John Hancock, as well as from Abbott’s sworn interrogatory responses in this action, that Abbott did not spend the Aggregate Spending Target on Program Related Costs over the four-year Program Term. I further understand, based upon the same sources, that Abbott did not spend the entire Aggregate Carryover Amount in 2005 (*i.e.*, the “subsequent year commencing immediately after the end of the Program Term”).

132. Notwithstanding these facts, Abbott has failed to refund to John Hancock one-third of the unspent Aggregate Carryover Amount as required under Section 3.3(b) of the Agreement.

*Abbott’s Obstruction of John Hancock’s
Attempt to Audit Abbott’s Compliance with the Agreement*

133. Section 2.5 of the Research Funding Agreement provides, in relevant part, that,

Abbott shall, and shall cause each Subcontractor to, maintain complete and accurate records ... for purposes of demonstrating compliance with the terms hereof, that fully and properly reflect all work done, results achieved and Program Related Costs expended in performance of the Research Program. The books and records of Abbott and each Subcontractor related to the Research Program ... shall be subject to copying, inspection and audit by (and at the expense of) John Hancock at any time and from time to time. Such audit shall occur on reasonable notice and during normal business hours by an independent auditor selected by John Hancock and reasonably acceptable to Abbott.... In the event that such audit reveals any material breach of Abbott’s responsibilities hereunder, Abbott shall (i) pay the

reasonable fees and expenses charged by such auditor, and
(ii) fully and promptly cure such breach.

134. In or about late 2003, I became concerned that Abbott was not complying with all of its obligations to John Hancock under the Agreement. Specifically, I had suspicions that Abbott may have intentionally withheld or misrepresented material facts concerning at least one Program Compound in the Agreement or prior to its execution.

135. When I raised my concerns regarding Abbott's conduct with James Tyree, then Abbott's Vice President of Global Licensing and New Business Development, Mr. Tyree vehemently denied any violations of the Agreement or intentional misconduct on Abbott's part. Mr. Tyree specifically told me, in part, that "Abbott takes any allegations of fraud very seriously and, after investigating the matter, has concluded that no basis exists for any such allegation by John Hancock." A true and accurate copy of Mr. Tyree's denial letter to me, dated November 20, 2003, is attached hereto as PLs' RQ.

136. In the face of Mr. Tyree's unequivocal denial of any wrongdoing on Abbott's part, I did not wish to assert a legal claim against Abbott for misrepresentation or fraud unless and until I was reasonably sure that a sufficient factual basis for such claims existed. Accordingly, I and others at John Hancock ultimately decided to exercise Hancock's right under Section 2.5 of the Research Funding Agreement to audit Abbott's compliance with the terms of that Agreement prior to asserting any claim for misrepresentation or fraud. It was my hope and expectation that the information obtained through such an audit would allow me and others at John Hancock to either confirm or dispel our suspicions regarding Abbott's conduct.

137. On April 12, 2004, I sent a letter to Mr. Tyree at Abbott notifying him of John Hancock's intention to undertake an audit of Abbott's compliance with the Agreement pursuant

to Section 2.5, and identifying The StoneTurn Group (“StoneTurn”) as John Hancock’s chosen independent auditor. A true and accurate copy of my notification letter to Mr. Tyree, dated April 12, 2004, is attached hereto as PLs’ NO. I included with my letter to Mr. Tyree a written description of the specific books and records related to the Research Program that John Hancock wished to examine in the first instance, along with a request that the materials be made available for examination by representatives of StoneTurn within thirty (30) days.

138. John Hancock’s attempt to independently audit Abbott’s compliance with the Research Funding Agreement ultimately was effectively stymied by Abbott. I understand and observed that Abbott responded to John Hancock’s demand for an audit of Abbott’s books and records pursuant to Section 2.5 of the Agreement by engaging in a protracted campaign to hinder, delay and obstruct Hancock and StoneTurn’s efforts to examine and assess Abbott’s compliance with terms of the Agreement.

139. On March 22, 2005, Abbott notified StoneTurn that Abbott purportedly had fulfilled its obligations with respect to John Hancock’s compliance audit, and that Abbott would not respond to any further requests from, or make any additional documents or information available to, Hancock or StoneTurn.

140. As a result of Abbott’s obstruction of John Hancock and StoneTurn’s efforts to audit Abbott’s compliance with the terms of the Agreement, Abbott never provided all of the documentation and information that was necessary for StoneTurn to complete its compliance audit on Hancock’s behalf.

141. As a result of Abbott’s obstruction of John Hancock and StoneTurn’s efforts to audit Abbott’s compliance with the terms of the Agreement, I and others at John Hancock were

unable to utilize the results of the audit process as an effective means to confirm or dispel our suspicions regarding Abbott's conduct.

142. The estimate of fees and expenses that John Hancock incurred and paid in connection with its failed compliance audit of Abbott is \$330 thousand, which sum includes StoneTurn's fees and expenses, as well as the legal fees and expenses of Choate, Hall & Stewart personnel associated with their unsuccessful attempts to administer and obtain Abbott's cooperation with the audit.

Abbott's Failure to Maximize the Value of ABT-518 and ABT-594

143. Section 4.3(d)(i) of the Research Funding Agreement requires that, if Abbott ceases development of any Program Compound, "as soon as is practicable Abbott shall maximize the commercial value, if any, of the Ceased Compound to both parties by out-licensing or divesting such Ceased Compound to a third party." Section 4.3(d)(iii) further provides that Abbott thereafter shall,

remunerate John Hancock based on sales of such Ceased Compound by the third party that has acquired or licensed the Ceased Compound ... in a manner most consistent with the allocation that would have applied hereunder had such Ceased Compound not been so out-licensed or divested....

144. I and others representing John Hancock demanded during negotiations that Abbott include the language Section 4.3(d) in the Agreement in order to ensure that, if Abbott decided to cease the development of any of the Program Compounds, Abbott would not simply put those compounds "on the shelf" and fail to out-license them because of their potential to compete with other compounds that Abbott was developing, or hoped to develop. I wanted Abbott's commitment that it would out-license or divest itself of each and every "Ceased

Compound” so that John Hancock could maximize its chances of at least recouping some or all of its investment in those compounds.

145. Abbott substantially ceased developing ABT-518 in 2001. Accordingly, ABT-518 is a “Ceased Compound” for purposes of Section 4.3(d) of the Agreement.

146. In the more than six years since 2001, Abbott has not out-licensed or divested ABT-518 to a third party.

147. Abbott substantially ceased developing ABT-594 in 2001. Accordingly, ABT-594 is a “Ceased Compound” for purposes of Section 4.3(d) of the Agreement.

148. In the more than six years since 2001, Abbott has not out-licensed or divested ABT-594 to a third party.

149. As a result of Abbott’s failure to out-license or divest ABT-518 and/or ABT-594 to one or more third parties as required under the terms of the Agreement, John Hancock has not been able to recoup any of its investment in those compounds or otherwise maximize the value of that investment.

150. As a result of Abbott’s failure to out-license or divest ABT-518 and/or ABT-594 to one or more third parties as required under the terms of the Agreement, John Hancock has not received any royalties or milestone payments for those compounds provided in that Agreement.

John Hancock's Damages

151. I believe that Abbott's breaches of the Agreement and fraud are of such a nature and of such importance that the Agreement would not have been made without them.

152. I believe that John Hancock has suffered actual monetary damages as a result of Abbott's breaches of the Agreement and fraud, including, but not limited to: lost or diminished potential royalties and milestone payments from Abbott on ABT-518, ABT-594 and ABT-773; lost or diminished potential royalties and milestone payments from any potential out-licensee of ABT-518 or ABT-594; the loss of Hancock's one-third share of the unspent portion of the Aggregate Carryover Amount; the loss of John Hancock's unnecessary Second Program Payment of \$54 million; and the professional and legal fees and expenses paid by Hancock in its failed attempt to audit Abbott's compliance with the Agreement.

153. I have examined the Amended Report of John Hancock's damages expert, Mr. Alan Friedman of CRA International, and believe that Mr. Friedman has properly calculated John Hancock's damages with reasonable certainty using reliable principles and methods applied reliably to sufficient facts and data.

Authentication of Additional Exhibits

154. The documents attached hereto as PLs' KQ, LF, LG, OC, OW, PM, PY, PZ, and QQ are true and accurate copies of records from the files of John Hancock that were made at or near the time of the matter recorded therein by me or by other people at Hancock having knowledge of the facts recorded, and that were made and are kept in the normal course of Hancock's regularly conducted business activities consist with Hancock's regular business practices.

Signed under the pains and penalties of perjury this 28th day of January, 2008.

/s/ Stephen J. Blewitt

Stephen J. Blewitt

CERTIFICATE OF SERVICE

I hereby certify that this document is being filed with the Court through the ECF system and that a copy will be sent electronically to counsel for defendant through the ECF system on January 28, 2008.

/s/ Richard C. Abati
Richard C. Abati (BBO No. 651037)

EX. 1

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Matrix Metalloproteinase Inhibitors Program

Descriptive Memorandum

May 2000

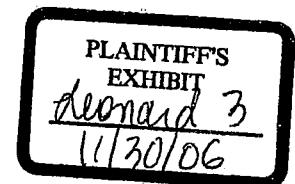
Abbott Laboratories

May 31st, 2000

Hancock_MMPI

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MMP1**Overview**

Abbott's Matrix Metalloproteinase Inhibitor (MMPi) program represents a novel therapeutic class, with the potential to alter the way that cancer is treated by preventing or modifying disease progression and/or metastases. This more "chronic" approach to therapy has the potential to transform cancer into a disease that patients live with, much like the effect of HIV protease inhibitors on patients with AIDS. It also has the potential to expand the cancer market significantly by increasing the average length of treatment and expanding the pool of patients eligible to receive therapy.

The MMPs comprise a family of enzymes that degrade a wide range of matrix protein substrates. High expression of these enzymes occurs in cancer and is associated with the ability of tumors to grow, invade, develop new blood vessels and metastasize.

MMP inhibitors (MMPis) may suppress the progression of tumors by several mechanisms:

- Suppress invasion/metastasis by blocking the membrane traversal and access to blood/lymphatic vessels
- Blocking the remodeling of extra-cellular matrix in the vicinity of primary tumors to prevent stroma-bound growth factors from stimulating tumor growth
- Blocking angiogenesis by preventing the proliferation and migration of endothelial cells and neovascularization of tumor.

Experimental evidence suggests that gelatinase A and gelatinase B are particularly important in tumor progression, consequently the project team has targeted gelatinase selective inhibitors for the treatment of cancer. Another reason for targeting highly gelatinase selective MMP inhibitors relates to the side effect profile exhibited by broad-spectrum agents like marimastat. Chronic administration of marimastat causes a dose-limiting side-effect characterized by severe joint pain and stiffness. Since these joint effects may be mediated by inhibition of other MMPs like fibroblast collagenase, highly gelatinase selective agents may be efficacious without producing dose-limiting side effects.

The MMP selectivity profile exhibited by ABT-518 distinguishes it from competitor's compounds. ABT-518 possesses sub-nanomolar inhibition potencies versus both gelatinase A and gelatinase B and is substantially more selective for the inhibition of the gelatinases over fibroblast collagenase than marimastat and prinomastat. Despite its high selectivity, ABT-518 demonstrates antitumor activity equal or superior to prinomastat. Inhibition of tumor growth is dose dependent in both syngeneic and xenograft models. ABT-518 is also effective in blocking vessel formation in a mouse model of angiogenesis. ABT-518 is a stable crystalline solid which can be synthesized in six steps (25% overall yield) from commercial starting material.

ABT-518 gives rise to sustained plasma concentrations following single oral dosing in monkeys, dogs and rats. Bioavailabilities range between 68 and 93% depending on formulation and species. Several metabolites are produced after repeated oral dosing of ABT-518, although their relative amounts varies with gender and species.

ABT-518 displays no meaningful effects in genotoxicity, cytotoxicity and ligand binding assays and its cardiovascular effects in dogs are unremarkable. ABT-518 produces no significant toxic effects in rats treated with 100 mg/kg/day over 28 days. Plasma concentrations generated by ABT-518 in these studies are at least 20-fold higher than those necessary to produce efficacy in cancer animal models. ABT-518 is therefore a compelling development candidate with the

Descriptive Memorandum: ABT - 518

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2

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potential to demonstrate antitumor effects superior to the MMP inhibitors currently undergoing clinical trials.

The market

Currently, cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market.

Global Sales by Market Segment (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
Hormone	4,414	4,784	4,884	5,000	5.2%
Cytotoxic	4,278	5,212	6,268	7,300	21.0%
Adjunctive	3,367	3,651	4,168	4,800	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

Sales by Region (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex- US	6,495	7,370	7,896	8,700	10.3%

Source: Datamonitor

Cytostatic agents have the potential to alter the way cancer is treated and presents opportunities for fundamentally new ways of approaching the disease. This cytostatic market does not yet exist, though success of more cytostatic "like" treatments, such as hormonal therapies for prostate and breast cancer, suggest that the market potential for cytostatic agents could be significant.

The ultimate commercial and clinical success of the MMPi will depend on the clinical benefit this product provides in key cancer types compared with current best therapy. These can be benefits provided by dosing this agent in addition to current therapy and/or as an alternative to best therapy, or as a new component of best therapy. All currently available products, including the market leaders such as Taxol, have significant shortcomings in their profiles.

However, as novel therapy, MMPis will probably be adopted initially as add-on the current chemotherapy. As benefits are proven and clinical experience is gained, these agents may be used in earlier stages of cancer and/or in conjunction with surgery or radiation to prevent the progression of any microscopic disease that remains.

The clinical targets identified for this compound include late stage pancreatic cancer, late stage NSCL cancer (on-label), with late stage ovarian and breast cancer as additional cancer types where efficacy has been demonstrated, but not filed. Other cancer types this compound may be efficacious in include SCL, colorectal, bladder, stomach and prostate. Targets will be refined as we know more about this compound's in-vivo activity.

The following tables summarize the key marketed competitive products by Indication (US data only):

Late Stage Breast	
Product	Share
Cyclophosphamide/Cytosar/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	18.25
Paclitaxel/Taxol/BMS	18.11
Trastuzumab/Herceptin/Genetech	11.26

Late Stage NSCL	
Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

Late Stage Ovarian	
Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/AIza	9.14
Cisplatin/Platinol/BMS	7.58

Late Stage Pancreas	
Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Efudex/ICN Pharma	21.0
Leucovorin/	10.7
Cisplatin/Platinol/BMS	4.72

Compounds in Development

The MMP inhibitor field is competitive. More than 30 firms have filed patents claiming small molecule MMP inhibitors over the past 5 years, and several companies have compounds in advanced clinical development. Abbott's compound may be 3rd or 4th to market and will have to demonstrate a competitive advantage to gain the share necessary to support the clinical development of this compound. Companies with compounds in advanced clinical development for the treatment of cancer include Agouron/Warner Lambert/Pfizer, British Biotechnology/Schering Plough and BMS and are listed below. Other companies are targeting this mechanism for arthritis.

MMPis In Clinical Development for Cancer

Compound	Company	Comments	Phase
Marimistat	British Biotechnology/ Schering Plough	Broad spectrum, dose limiting toxicity. Activity seen in gastric cancer, but negative results in pancreatic.	III
Prinomastat	Agouron/ Warner Lambert/ Pfizer	Moderate gelatinase selectivity, dose limiting toxicity. May be dosing sub-optimally to avoid toxicity. Efficacy data not available.	III
BMS 275291	BMS	Broad spectrum, joint effects seen in Phase I studies.	II

Bayer recently dropped development of BAY 12-9566 due to concerns about potential toxicity. Recent results from a study with marimistat in pancreatic cancer, where adding marimistat to Gemzar resulted in no survival advantage, has led to speculation that MMPis may be more applicable in less aggressive cancer types or earlier stages of the disease. Alternatively, it could be a reflection of the inability to examine higher doses of marimastat due to joint effects.

The joint effects produced by the compounds listed above almost certainly preclude their long-term use, limit compliance and reduce optimal efficacy. Any MMP inhibitor that lacks these side effects will possess a substantial competitive advantage. The musculoskeletal effect produced by marimastat and prinomastat in cancer patients is typically described as arthralgia, myalgia and tendinitis, which occurs predominately in the upper limbs. While mild cases respond to analgesics, interrupting therapy for a period of approximately 2 weeks is necessary when the condition is less well tolerated.

Although Abbott's timing to market is not optimal, the shortcomings of the competitive products provide an opportunity for a compound with an improved SE or efficacy profile. Current animal models seem to predict Abbott's compound is superior to those currently in clinical trials, and has the potential to be best in class.

Product profile

The objective of a product profile at this time in the product's development is to provide a target for the types of attributes that will be required to be commercially successful. This profile is based on market research with oncologists and consultation with opinion leaders. This profile will continue to be refined as more is known about this product's profile, development of competitive products and the market continues to evolve.

	Base	Optimal
Efficacy	ABT-518, alone or in combination with best therapy, provides at least one of the following benefits in at least one solid tumor type: <ul style="list-style-type: none"> • Increased survival • Tumor regression • Improved quality of life • Increased time to tumor/disease progression 	Provides more than one of the efficacy benefits outlined.
Competitive advantage	ABT-518 will need to demonstrate a clinically significant advantage in efficacy (see parameters above) or additive synergistic activity with current/competitive agents or clinically significant advantage in side-effect profile relative to other MMPi agents.	Same
Administration	Convenient administration relative to competitive agents.	Same plus reimbursement in US market.
COGS	A finished cost of goods that is consistent with at least an 80% standard manufacturing margin.	A finished cost of goods that is consistent with at least a 80% standard manufacturing margin.

Marketing overview

Product Usage: Physicians have indicated that they would use MMPis initially in their more refractory patients, as follow-on or add-on to current best therapy (chemo or surgical). With experience and clinical evidence, they would be willing to use these agents in earlier stages of the disease, where they perceived the greatest benefit to be. The MMPi was regarded as a maintenance therapy to be used in early disease or after primary therapy as a prophylactic process to prevent the spread of malignancy.

Product Benefits/Efficacy: Physicians are looking for improvements in time to tumor progression and prevention of metastases with cytostatic agents. The MMPi mechanism has more recently been implicated as having an even more active role in cancer pathogenesis, from preventing primary tumor growth to anti-angiogenic properties. Positive results from competitive agents, such as maimistat in gastric cancer, provides proof of principle for this mechanism.

Side Effects: The proposed safety profile of MMPis (excluding joint toxicity) may enhance usage, as the dose limiting toxicity profiles of most of the other available agents has established a much lower hurdle for demonstrating a preferred profile. However, as chronic therapy, MMPis may have to demonstrate a cleaner profile than cytotoxic agents do to ensure compliance. As the 3rd or 4th MMPi to market, SE hurdles will be even higher for this compound. As a critical Go/No Go decision point, the joint toxicity of this compound will be evaluated in an expanded Phase I multi-dose study.

Dosing: Discovery is currently targeting an oral dosage form. In general, oral therapies are acknowledged by physicians and patients as being more convenient to the patient. Chronic oral dosing may also reduce overall costs, as infusion support products and personnel would not be required, enhancing pharmacoeconomic evidence.

Descriptive Memorandum: ABT - 518

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COGS: Initial estimates on finished cost of drug suggest that drug costs will not be significant for this compound. With the pricing flexibility in the US market, PPD should be able to get more than 90% margin on this product.

Off-label use: Off label use accounts for between 30-60% of an oncology product's usage. Off-label use is driven by publication of clinical trial results in credible journals, listing in key compendia and/or a peer's experience with the product. Therefore, development spend for off-label use is considerably less than the spend required for regulatory approval of an indication. However, promotion of these off-label uses is limited.

Competition: As the 3rd or 4th MMPI to market, Abbott's compound will need to demonstrate a meaningful clinical advantage over compounds that are in more advanced development. Strict Go/No Go criteria will determine if the MMPI can meet these hurdles. If they cannot be met, the compound will not move forward.

Development/Regulatory: With a new class of compounds, there is not a clearly defined clinical development path or regulatory guidelines for reference. This hurdle is similar for all the competitive products, but increases the overall development risk profile for these agents. However, with several MMPIs in late stage development, Abbott can learn from their experience.

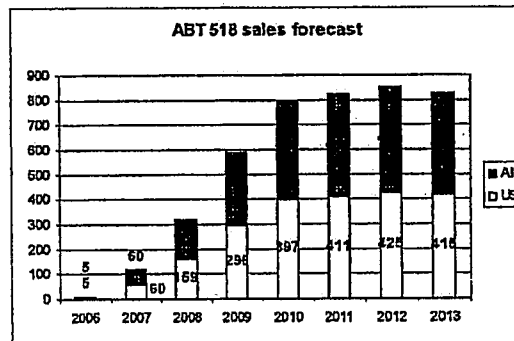
Other Approaches: Other "cytostatic" approaches may present a competitive threat if they are used as substitutes. Due to the complexity of the pathogenesis of cancer, it is more likely that these agents will be used in combinations, but incremental benefits may become more difficult to demonstrate as the number of products and approaches multiply. This will require additional studies, as these other classes become part of standard cancer treatment. However, this threat is not unique to this compound.

Pricing: The treatment of cancer is expensive, so there is the potential for a great deal of pricing flexibility in this market. However, as an oral therapy in the US market, there may be additional downward price pressure for this agent. There is also an increasing emphasis on cost-effectiveness studies that will need to be addressed in the development plan.

Dosing: Discovery is currently targeting an oral dosage form. In general, oral therapies are preferred by physicians and patients because of the convenience to the patient. However, this form may not be the best choice for some people who already have certain digestive system symptoms (vomiting, diarrhea, or severe nausea), cannot swallow liquids or pills, or cannot remember when or how many pills to take. Additionally, in the US market there are several unique factors that currently do not favor oral therapies. Novel oral therapies are not currently reimbursed by Medicare, a significant payer for the oncology patient population. Also, 40-60% of a community oncologist's income is generated through the administration of IV drugs. An oral therapy would not be a source of revenue to the physician.

Financial Projections

A product forecast was developed for the US and ex-US markets.

**Clinical Studies**

Clinical studies across a wide range of solid tumors will be initiated, including but not limited to breast cancer, non small cell lung cancer, ovarian cancer, pancreatic cancer, etc...

Final indications pursued will depend from the results of the phase II studies.

Patent Status

The patent is estimated to expire in August of 2018.

Descriptive Memorandum: ABT - 518

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8

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ABBT246454

EX. 2

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ABT - 518

Descriptive Memorandum

February 2001

Abbott Laboratories

November 1st, 2000

Hancock_MMPI

Highly Confidential

ABBT245829

MMPI*Overview*

Abbott's Matrix Metalloproteinase Inhibitor (MMPI) program represents a novel therapeutic class, with the potential to alter the way that cancer is treated by preventing or modifying disease progression and/or metastases. This more "chronic" approach to therapy has the potential to transform cancer into a disease that patients live with, much like the effect of HIV protease inhibitors on patients with AIDS. It also has the potential to expand the cancer market significantly by increasing the average length of treatment and expanding the pool of patients eligible to receive therapy.

The MMPs comprise a family of enzymes that degrade a wide range of matrix protein substrates. High expression of these enzymes occurs in cancer and is associated with the ability of tumors to grow, invade, develop new blood vessels and metastasize.

MMP inhibitors (MMPIs) may suppress the progression of tumors by several mechanisms:

- Suppress invasion/metastasis by blocking the membrane traversal and access to blood/lymphatic vessels
- Blocking the remodeling of extra-cellular matrix in the vicinity of primary tumors to prevent stroma-bound growth factors from stimulating tumor growth
- Blocking angiogenesis by preventing the proliferation and migration of endothelial cells and neovascularization of tumor.

Experimental evidence suggests that gelatinase A and gelatinase B are particularly important in tumor progression, consequently the project team has targeted gelatinase selective inhibitors for the treatment of cancer. Another reason for targeting highly gelatinase selective MMP inhibitors relates to the side effect profile exhibited by broad-spectrum agents like marimastat. Chronic administration of marimastat causes a dose-limiting side-effect characterized by severe joint pain and stiffness. Since these joint effects may be mediated by inhibition of other MMPs like fibroblast collagenase, highly gelatinase selective agents may be efficacious without producing dose-limiting side effects.

The MMP selectivity profile exhibited by ABT-518 distinguishes it from competitor's compounds. ABT-518 possesses sub-nanomolar inhibition potencies versus both gelatinase A and gelatinase B and is substantially more selective for the inhibition of the gelatinases over fibroblast collagenase than marimastat and prinomastat. Despite its high selectivity, ABT-518 demonstrates antitumor activity equal or superior to prinomastat. Inhibition of tumor growth is dose dependent in both syngeneic and xenograft models. ABT-518 is also effective in blocking vessel formation in a mouse model of angiogenesis. ABT-518 is a stable crystalline solid which can be synthesized in six steps (25% overall yield) from commercial starting material.

ABT-518 gives rise to sustained plasma concentrations following single oral dosing in monkeys, dogs and rats. Bioavailabilities range between 68 and 93% depending on formulation and species. Several metabolites are produced after repeated oral dosing of ABT-518, although their relative amounts varies with gender and species.

ABT-518 displays no meaningful effects in genotoxicity, cytotoxicity and ligand binding assays and its cardiovascular effects in dogs are unremarkable. ABT-518 produces no significant toxic effects in rats treated with 100 mg/kg/day over 28 days. Plasma concentrations generated by ABT-518 in these studies are at least 20-fold higher than those necessary to produce efficacy in cancer animal models. ABT-518 is therefore a compelling development candidate with the

potential to demonstrate antitumor effects superior to the MMP inhibitors currently undergoing clinical trials. Phase 1 clinical trials in cancer patients began March 2001.

The market

Currently, cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market.

Global Sales by Market Segment (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
Hormone	4,414	4,784	4,884	5,000	5.2%
Cytotoxic	4,278	5,212	6,268	7,300	21.0%
Adjunctive	3,367	3,651	4,166	4,900	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

Sales by Region (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex- US	6,495	7,370	7,896	8,700	10.3%

Source: Datamonitor

Cytostatic agents have the potential to alter the way cancer is treated and presents opportunities for fundamentally new ways of approaching the disease. This cytostatic market does not yet exist, though success of more cytostatic "like" treatments, such as hormonal therapies for prostate and breast cancer, suggest that the market potential for cytostatic agents could be significant.

The ultimate commercial and clinical success of the MMPI will depend on the clinical benefit this product provides in key cancer types compared with current best therapy. These can be benefits provided by dosing this agent in addition to current therapy and/or as an alternative to best therapy, or as a new component of best therapy. All currently available products, including the market leaders such as Taxol, have significant shortcomings in their profiles.

However, as novel therapy, MMPs will probably be adopted initially as add-on the current chemotherapy. As benefits are proven and clinical experience is gained, these agents may be used in earlier stages of cancer and/or in conjunction with surgery or radiation to prevent the progression of any microscopic disease that remains.

The clinical targets identified for this compound include late stage pancreatic cancer, late stage NSCL cancer (on-label), with late stage ovarian and breast cancer as additional cancer types where efficacy has been demonstrated, but not filed. Other cancer types this compound may be efficacious in include SCL, colorectal, bladder, stomach and prostate. Targets will be refined as we know more about this compound's in-vivo activity.

The following tables summarize the key marketed competitive products by indication (US data only):

Late Stage Breast	
Product	Share
Cyclophosphamide/Cytoxan/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	16.25
Paclitaxel/Taxol/BMS	16.11
Trastuzumab/Herceptin/Genetech	11.26

Late Stage NSCL	
Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

Late Stage Ovarian	
Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/Alza	9.14
Cisplatin/Platinol/BMS	7.58

Late Stage Pancreas	
Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Efudex/ICN Pharma	21.0
Leucovorin/	10.7
Cisplatin/Platinol/BMS	4.72

Compounds in Development

The MMP inhibitor field is competitive. More than 30 firms have filed patents claiming small molecule MMP inhibitors over the past 5 years, and several companies have compounds in advanced clinical development. Abbott's compound may be 3rd or 4th to market and will have to demonstrate a competitive advantage to gain the share necessary to support the clinical development of this compound. Companies with compounds in advanced clinical development for the treatment of cancer include Agouron/Warner Lambert/Pfizer, British Biotechnology/Schering Plough and BMS and are listed below. Other companies are targeting this mechanism for arthritis.

MMPis in Clinical Development for Cancer

Compound	Company	Comments	Phase
Marimistat	BritishBiotechnology/ Schering Plough	Broad spectrum, dose limiting toxicity. Activity seen in gastric cancer, but negative results in pancreatic.	III
Prinomastat	Agouron/ Warner Lambert/ Pfizer	Moderate gelatinase selectivity, dose limiting toxicity. May be dosing sub-optimally to avoid toxicity. Efficacy data not available.	III
BMS 275291	BMS	Broad spectrum, joint effects seen in Phase I studies.	II

Bayer recently dropped development of BAY 12-9566 due to concerns about potential toxicity. Recent results from a study with marimistat in pancreatic cancer, where adding marimistat to Gemzar resulted in no survival advantage, has led to speculation that MMPis may be more applicable in less aggressive cancer types or earlier stages of the disease. Alternatively, it could be a reflection of the inability to examine higher doses of marimastat due to joint effects.

The joint effects produced by the compounds listed above almost certainly preclude their long-term use, limit compliance and reduce optimal efficacy. Any MMP inhibitor that lacks these side effects will possess a substantial competitive advantage. The musculoskeletal effect produced by marimastat and prinomastat in cancer patients is typically described as arthralgia, myalgia and tendinitis, which occurs predominately in the upper limbs. While mild cases respond to analgesics, interrupting therapy for a period of approximately 2 weeks is necessary when the condition is less well tolerated.

Although Abbott's timing to market is not optimal, the shortcomings of the competitive products provide an opportunity for a compound with an improved SE or efficacy profile. Current animal models seem to predict Abbott's compound is superior to those currently in clinical trials, and has the potential to be best in class.

Product profile

The objective of a product profile at this time in the product's development is to provide a target for the types of attributes that will be required to be commercially successful. This profile is based on market research with oncologists and consultation with opinion leaders. This profile will continue to be refined as more is known about this product's profile, development of competitive products and the market continues to evolve.

	Base	Optimal
Efficacy	ABT-518, alone or in combination with best therapy, provides at least one of the following benefits in at least one solid tumor type: <ul style="list-style-type: none"> • Increased survival • Tumor regression • Improved quality of life • Increased time to tumor/disease progression 	Provides more than one of the efficacy benefits outlined.
Competitive advantage	ABT-518 will need to demonstrate a clinically significant advantage in efficacy (see parameters above) or additive synergistic activity with current/competitive agents or clinically significant advantage in side-effect profile relative to other MMPi agents.	Same
Administration	Convenient administration relative to competitive agents.	Same plus reimbursement in US market.
COGS	A finished cost of goods that is consistent with at least an 80% standard manufacturing margin.	A finished cost of goods that is consistent with at least a 90% standard manufacturing margin.

Marketing overview

Product Usage: Physicians have indicated that they would use MMPis initially in their more refractory patients, as follow-on or add-on to current best therapy (chemo or surgical). With experience and clinical evidence, they would be willing to use these agents in earlier stages of the disease, where they perceived the greatest benefit to be. The MMPi was regarded as a maintenance therapy to be used in early disease or after primary therapy as a prophylactic process to prevent the spread of malignancy.

Product Benefits/Efficacy: Physicians are looking for improvements in time to tumor progression and prevention of metastases with cytostatic agents. The MMPi mechanism has more recently been implicated as having an even more active role in cancer pathogenesis, from preventing primary tumor growth to anti-angiogenic properties. Positive results from competitive agents, such as marimistat in gastric cancer, provides proof of principle for this mechanism.

Side Effects: The proposed safety profile of MMPis (excluding joint toxicity) may enhance usage, as the dose limiting toxicity profiles of most of the other available agents has established a much lower hurdle for demonstrating a preferred profile. However, as chronic therapy, MMPis may have to demonstrate a cleaner profile than cytotoxic agents do to ensure compliance. As the 3rd or 4th MMPi to market, SE hurdles will be even higher for this compound. As a critical Go/No Go decision point, the joint toxicity of this compound will be evaluated in an expanded Phase I multi-dose study.

Dosing: Discovery is currently targeting an oral dosage form. In general, oral therapies are acknowledged by physicians and patients as being more convenient to the patient. Chronic oral dosing may also reduce overall costs, as infusion support products and personnel would not be required, enhancing pharmacoeconomic evidence.

COGS: Initial estimates on finished cost of drug suggest that drug costs will not be significant for this compound

Off-label use: Off label use accounts for between 30-60% of an oncology product's usage. Off-label use is driven by publication of clinical trial results in credible journals, listing in key compendia and/or a peer's experience with the product. Therefore, development spend for off-label use is considerably less than the spend required for regulatory approval of an indication. However, promotion of these off-label uses is limited.

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Clinical Studies

Clinical studies across a wide range of solid tumors will be initiated, including but not limited to breast cancer, non small cell lung cancer, ovarian cancer, pancreatic cancer, etc...

Final indications pursued will depend from the results of the phase II studies.

EX. 13



Daphne L. Pals
Senior Counsel

Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-0149
Telephone: (847) 938-3747
Telecopy: (847) 938-1306

September 20, 2001

John Hancock Life Insurance Company
200 Clarendon Street, T-57
Boston, MA 02117
Attention: Bond & Corporate Finance Group
Fax: 617-572-1628

Re: Research Funding Agreement dated as of March 13, 2001
Termination of MMPI Program and ABT-518

Dear Steve,

This is to advise you that Abbott has refocused its efforts in cancer discovery and, as a result, has made the decision to terminate the MMPI Program, which includes Program Compound ABT-518. There will not be any further funding of ABT-518 or the MMPI Program, except as is required to continue to collect data on already enrolled patients.

Section 4.3(c) of the Agreement is not applicable as the cessation of the development of ABT-518 was not the result of Abbott's acquisition of a Replacement Compound. Abbott will attempt to maximize the commercial value, if any, of ABT-518 as required under Section 4.3(d).

Phil Deemer has attempted to schedule a meeting with you to discuss the termination for the MMPI Program, as well as introduce you to Tom Lyons, our new controller, Global Pharmaceuticals Research and Development. Unfortunately, due to scheduling problems, that meeting has not yet occurred. We look forward to scheduling that meeting soon.

I hope you are doing well.

Sincerely,

Daphne Pals
Senior Counsel

cc: John Hancock Life Insurance Company
200 Clarendon Street, T-50
Boston, MA 02117
Attention: Investment Law Division
Fax: 617-572-9268

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ABBT 0025972

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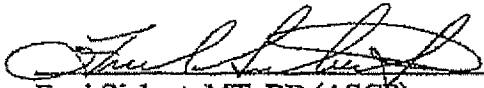
EX. 16

ABBOTT LABORATORIES
Clinical Protocol

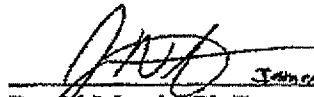
**A Randomized, Double Blind, Placebo-Controlled, Comparison
of the Safety and Efficacy of ABT-594 to Placebo in Subjects
with Painful Diabetic Polyneuropathy**

Protocol M99-114


February 8, 2000


Fred Siebert, MT-BB (ASCP)
Senior Clinical Research Associate, Analgesia Venture


2/10/2000
Date


David Morris, Ph.D.
Manager, Clinical Statistics


2-11-00
Date


Walid Awni, Ph.D.
Manager, Clinical Pharmacokinetics

2/11/00
Date


Bruce G. McCarthy, M.D.
Associate Medical Director, Analgesia Venture

2/10/00
Date


Christopher J. Silber, M.D.
Venture Head, Analgesia Venture

2/10/00
Date

PLAINTIFF'S
EXHIBIT
MCCARTHY

68

3/16/07

 **Abbott Laboratories**

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ABT-594
Protocol M99-114
February 8, 2000

i

1.0 Title Page

Abbott Laboratories
Analgesia Venture, D48Q
Clinical Study

**A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety
and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic
Polyneuropathy**

ABT-594/M99-114
February 8, 2000

Development Phase: II

Investigators: Multicenter Trial

Estimated Date of First Subject to be Dosed: April 2000

Estimated Date of Last Subject to Complete Dosing: November 2000

Sponsor/Emergency Contact: Christopher J. Silber, M.D.
Venture Head,
Analgesia Venture
Phone: (847) 938-5236, Fax: (847) 938-5258
Department 48Q, Building AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-6193

This study will be conducted in compliance with Good Clinical Practice, including
the archiving of essential documents.

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ABT-594
Protocol M99-114
February 8, 2000

ii

2.0 Study Synopsis

Name of Company: Abbott Laboratories Name of Finished Product: ABT-594 Hard Gelatin Capsule (HGC) Name of Active Ingredient: ABT-594	Individual Study Table Referring to Part of the Dossier: Not Applicable (N/A) Volume: N/A Page: N/A	(For National Authority Use Only)
Title of Study: A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy		
Investigator(s): Multicenter Study		
Study Center(s): 30		
Publication (reference): N/A		
Study Period (years): Estimated Date of First Subject to be Dosed: April, 2000 Estimated Date of Last Subject to Complete Dosing: November, 2000		Phase of Development: II
Objectives: The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy, have an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and have ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert) at the Baseline Visit.		
Methodology: This is a Phase II, randomized, double-blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who have painful diabetic polyneuropathy. Approximately 320 subjects will be assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg, or placebo BID for 49 days on an outpatient basis. Approximately 30 sites will be recruited in order to enroll 320 subjects who meet entry criteria for this study. Prior to any study-specific procedures at the Screening Visit, an informed consent will be signed and study eligibility determined.		

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ABT-594
Protocol M99-114
February 8, 2000

iii

Methodology: (Continued)

Prior to study drug administration, subjects will have discontinued all analgesic medications (at least 7 days prior to the Baseline Pain Assessment Phase) and have completed the 7-day Baseline Pain Assessment Phase. Following the Baseline Pain Assessment Phase, subjects who meet entry criteria, will be randomized to a dose of study medication for 49 days (Primer and Treatment Phases). During the Treatment Phase, subjects will return to the site for Treatment Visits I, II, III and IV (Days 14, 21, 35 and 49, respectively). During the Primer and Treatment Phases, subjects will be allowed to take up to 3 grams of acetaminophen per day or up to 6 grams of acetaminophen per week (but will not be allowed to take acetaminophen within 24 hours prior to a Treatment Visit). Subjects will complete diary-based assessments of their diabetic polyneuropathy pain each day from the 7 days prior to study drug administration (Baseline Pain Assessment Phase) through Day 49 of study drug administration. In addition, subjects will undergo site-based assessments of their neuropathy pain at the Baseline Visit and Treatment Visits I, II, III and IV. Subjects will discontinue study drug administration after Treatment Visit IV and return to the site for the Follow-Up visit 7-10 days later. See Figure 9.1a, Study Schematic, for additional study layout information.

Efficacy and safety assessments will include: the Pain Rating Scale (11-Point Likert), the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), and Subject and Clinician Global Impression of Change.

No. of Subjects: 320

Diagnosis and Main Criteria for Inclusion:

A subject may be randomized in this study provided that he/she meets all of the Inclusion Criteria outlined below and does not meet any of the Exclusion Criteria in Section 9.3.2.

- Prior to any study specific procedure, voluntary written informed consent must be obtained from the subject after the purpose and nature of the study have been explained.
- The subject must be age 18 or older and in relatively good health with a recent stable medical history.
- The subject's weight must be \leq 265 pounds.
- A female subject must be non-lactating and:
 - of non-childbearing potential (either postmenopausal for at least 1 year or surgically sterile, including tubal ligation),
 - OR
 - of childbearing potential using oral or barrier contraceptive methods for at least 2 months preceding randomization (and must continue contraceptive method through the course of the study).

All female subjects must have a negative β subunit human chorionic gonadotropin (β -hCG) at the Baseline Visit. Female subjects of childbearing potential must have a negative β -hCG at all Treatment Visits.

- The subject must have a diagnosis of diabetes mellitus (Type I or Type II) and a diagnosis of distal symmetric diabetic polyneuropathy.
- The subject must have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy.

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ABT-594
Protocol M99-114
February 8, 2000

iv

- The location and quality of the pain under study are consistent with distal symmetric diabetic polyneuropathy in the opinion of the investigator.
- The subject has distal symmetric diabetic polyneuropathy symptoms (including pain) which have been stable for at least the last 3 months prior to the Screening Visit (defined by the opinion of the investigator).
- The subject must have an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) everyday during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-point Likert Scale) at the Baseline Visit.

Test Product(s): ABT-594 75 μ g HGC (Formulation A-2)

Dose: ABT-594 150 μ g, 225 μ g, or 300 μ g BID (Section 9.4)

Mode of Administration: Oral

Batch Number:

Study Drug	Drug Product Lot Number
ABT-594 75 μ g HGC	58-293-AR

Duration of Treatment: 49 days

Reference Therapy: Placebo for ABT-594 HGC No. 1 Light Gray Opaque (Starch)

Dose: Placebo to match test product (see Section 9.4)

Mode of Administration: Oral

Batch Number:

Study Drug	Drug Product Lot Number
Placebo for ABT-594 HGC	55-243-AR-01

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ABT-594
Protocol M99-114
February 8, 2000

v

Criteria for Evaluations:

Efficacy:

The primary efficacy measurement will be the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. Additionally, change from baseline to each scheduled evaluation will be analyzed in a similar manner. The baseline pain score for the diary data is defined as the average of the last 7 pain scores prior to Day 1 of the study.

Change from baseline to final and each evaluation will be calculated for each of the following secondary efficacy variables:

- Site-Based Pain Rating Scale (11-Point Likert)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health] PCS, and MCS.

The efficacy evaluations recorded at the Baseline Visit will be used as the baseline score for efficacy evaluations assessed at the investigative site.

Safety:

Safety will be assessed by medical history, physical exam, vital signs, electrocardiogram (ECG), clinical laboratory testing, and adverse event monitoring.

Pharmacokinetics:

Blood samples for ABT-594 plasma assay will be taken from all subjects at Treatment Visits I and IV. For the subset of subjects who undergo intensive pharmacokinetic sampling at Treatment Visits I and IV, values of AUC, C_{max} , and C_{trough} will be determined.

Statistical Methods:

For all safety and efficacy analyses, the primary comparisons will be between each ABT-594 dose and placebo.

Demographic and other baseline characteristic variables will be analyzed to assess the comparability of the treatment groups.

The primary and secondary efficacy variables, including change from baseline diary and site based rating will be analyzed by using appropriate parametric and nonparametric methods. The final global evaluation scores, (Subject and Clinician) will be compared using Cochran-Mantel-Haenszel methodology.

Dose response for ABT-594 will be explored, with and without placebo included. Other efficacy analyses will be performed as appropriate.

Treatment emergent adverse events will be summarized by body system and COSTART term and compared using Fisher's exact test.

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ABT-594
Protocol M99-114
February 8, 2000

vi

Statistical Methods: (Continued)

Mean change from baseline to minimum, maximum and final values will be summarized for clinical laboratory, vital sign and ECG data. Additionally, clinical laboratory data identified as below or above limits will be flagged in the data listings. Furthermore, laboratory results which satisfy the criteria for limits for statistical analysis will be identified.

To assess dose proportionally and time invariance (from Visit I to Visit IV), dose-normalized C_{trough} and log-transformed dose-normalized AUC, and C_{max} from the subset of subject participating in intensive pharmacokinetic sampling will be subjected to a mixed effects model analysis with effects for dose level, visit, relevant covariates, and perhaps study center. The logarithmic transformation will be employed for AUC and C_{max} . An exploratory analysis will also be performed on the data set obtained from all subjects.

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ABBT0065824

ABT-594
Protocol M99-114
February 8, 2000

vii

3.0 Table of Contents

	Page
1.0 Title Page	i
2.0 Study Synopsis	ii
3.0 Table of Contents	vii
4.0 List of Abbreviations and Definitions of Terms	xi
5.0 Ethics	1
5.1 Institutional Review Board or Independent Ethics Committee ..	1
5.2 Ethical Conduct of the Study	1
5.3 Subject Information and Consent	1
5.4 Subject Confidentiality	2
6.0 Investigators and Study Administrative Structure	3
6.1 Investigative Sites	3
6.2 Sponsor Information	3
6.3 Contract Research Organization	3
6.4 Clinical Supply Management	3
6.5 Central Laboratory	4
6.6 Administrative Structure	5
7.0 Introduction	6
7.1 Analgesia Today	6
7.2 ABT-594	6
8.0 Study Objectives	9
9.0 Investigational Plan	10
9.1 Overall Study Design and Plan: Description	10
9.2 Discussion of Study Design, Including the Choice of Control Groups	14
9.3 Selection of Study Population	14

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Confidential
ABBT0065825

ABT-594
Protocol M99-114
February 8, 2000

viii

Table of Contents (Continued)

	Page
9.3.1 Inclusion Criteria	14
9.3.2 Exclusion Criteria	15
9.3.3 Removal of Subjects from Therapy	16
9.4 Treatments	17
9.4.1 Treatments Administered	17
9.4.2 Identity of Investigational Products	19
9.4.2.1 Packaging and Labeling	19
9.4.2.2 Storage and Disposition of Supplies	19
9.4.2.3 Drug Accountability	20
9.4.3 Method of Assigning Subjects to Treatment Groups	20
9.4.4 Selection of Doses in the Study	21
9.4.5 Selection and Timing of Dose for Each Subject	21
9.4.6 Blinding	21
9.4.7 Prior and Concomitant Therapy	21
9.4.8 Treatment Compliance	22
9.5 Efficacy, Pharmacokinetic and Safety Variables and Other Study Procedures	23
9.5.1 Efficacy and Safety Measurements Assessed and Flow Charts	23
9.5.1.1 Efficacy Measurements	25
9.5.1.2 Safety Measurements and Procedures	26
9.5.2 Appropriateness of Measurements	34
9.5.3 Efficacy Variables	34
9.5.3.1 Primary Variable(s)	35
9.5.3.2 Secondary Variable(s)	35
9.5.4 Drug Concentration Measurements	35

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Confidential
ABBT0065826

ABT-594
Protocol M99-114
February 8, 2000

ix

Table of Contents (Continued)

	Page
9.5.4.1 Collection, Processing and Storage of Blood Samples for ABT-594 Plasma Assay	35
9.5.4.2 Additional Pharmacokinetic Sampling	36
9.5.4.3 Shipment of Plasma Samples	37
9.5.5 Blood Samples for Genetic Polymorphism Analysis	37
9.6 Data Quality Assurance	38
9.7 Statistical Methods and Determination of Sample Size	39
9.7.1 Statistical and Analytical Plans	39
9.7.1.1 Data Sets Analyzed	40
9.7.1.2 Demographic and Other Baseline Characteristics	40
9.7.1.3 Efficacy Analyses	40
9.7.1.4 Safety Analyses	43
9.7.2 Determination of Sample Size	44
9.7.3 Pharmacokinetics/Pharmacodynamics	44
9.8 Changes in the Conduct of the Study or Planned Analyses	45
9.8.1 Protocol Changes	45
10.0 Protocol Deviations	46
11.0 Use of Information and Publication	46
12.0 Completion of The Study	47
13.0 Investigator's Agreement	48
14.0 References	49

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Confidential
ABBT0065827

ABT-594
Protocol M99-114
February 8, 2000

x

Table of Contents (Continued)

	Page
List of Tables	
Table 9.4.1a	ABT-594 Dose Escalation 18
Table 9.4.1b	Number and Type of Capsules by Treatment Regimen 18
Table 9.4.2a	Identity of Investigational Products 19
Table 9.5a	Study Procedures Flow Chart 24
Table 9.5b	Clinical Laboratory Tests 28
Table 9.5c	Definitions for Investigator Rating of Adverse Event Severity 30
Table 9.5d	Definitions for Investigator Assessment of Adverse Event Relationship to Study Drug 31

List of Figures	
Figure 6.6a	Administrative Structure 5
Figure 9.1a	Study Schematic 13

List of Appendices	
Appendix A	Documents Required Prior to Initiation of the Study 50
Appendix B	Declaration of Helsinki 51
Appendix C	Responsibilities of the Clinical Investigator 55
Appendix D	Elements of the Consent Form 56
Appendix E	Sample Abbott Laboratories Drug Accountability Form Study M99-114 59
Appendix F	Pain Assessments 60
Appendix G	Neuropathic Pain Scale 61
Appendix H	Subject Global Impression of Change and Clinician Global Impression of Change 63
Appendix I	Laboratory Determinations, Vital Signs and Electrocardiogram Variables for Statistical Analysis 64

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Confidential
ABBT0065828

ABT-594
Protocol M99-114
February 8, 2000

xi

4.0 List of Abbreviations and Definitions of Terms

ABT-594	[(R)-5-(2-azetidinylmethoxy)-2-chloropyridine] or A-165594
CSI	Clinical Supplies Invoice
HGC	Hard Gelatin Capsules
IVRS	Interactive Voice Response System
nAChRs	Neuronal nicotinic acetylcholine receptors
NPRO	New Product Research Order
NPS	Neuropathic Pain Scale

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Confidential
ABBT0065829

ABT-594
Protocol M99-114
February 8, 2000

1

5.0 Ethics

5.1 Institutional Review Board or Independent Ethics Committee

Good Clinical Practice (GCP) requires that approval be obtained from a research committee (e.g., Institutional Review Board [IRB], Independent Ethics Committee [IEC]), prior to participation of human subjects in research. The investigator will obtain a duly constituted IRB/IEC review and approval of the protocol, informed consent form and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects). Abbott Laboratories will receive documentation of the study approval, the signed signature page from the study protocol, a signed Abbott Financial Disclosure form, subject informed consent document, a current investigator curriculum vitae, a signed Food and Drug Administration (FDA) Form 1572 or equivalent document, a list of members of the IRB committee and their qualifications and affiliations prior to authorizing the shipment of study drug supplies to the site. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. No annual IRB re-approvals are anticipated since the study should be completed within one year. A complete list of documents required prior to initiation of the study is located in Appendix A.

5.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, GCP, FDA regulations governing clinical study conduct, ethical principles that have their origin in the Declaration of Helsinki (1996 Version, Appendix B) and all applicable local regulations. The investigator must assure that the study will be conducted in accordance with prevailing local laws and customs or comply with the provisions as stated in the FDA guidelines. Responsibilities of the Investigator are specified in Appendix C.

5.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement will be reviewed and

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Confidential
ABBT0065830

ABT-594
Protocol M99-114
February 8, 2000

2

signed and dated by the subject and the person who administered the informed consent. A copy of the informed consent form will be given to the subject and a copy will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. Elements of an Informed Consent are specified in Appendix D.

5.4 Subject Confidentiality

All reports and communications relating to subjects in the study will identify each subject only by the subject's initials (first, middle, last) and by the subject's randomization number. Case report forms (CRF) will be used to transmit the information collected in the performance of this study to Abbott Laboratories and to governmental agencies. Portions of the subject's medical records pertinent to the study will be reviewed by Abbott Laboratories personnel or their designee and possibly by government personnel to assure adequate source documentation, accuracy, and completeness of the CRFs.

The site will collect information on the subject per International Council on Harmonization (ICH) requirements, including subject name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who can be contacted in an emergency should also be recorded. This information will be treated with strict adherence to professional standards of confidentiality and will be filed at the site according to the record retention guidelines outlined in Section 12.0.

Neither the subject, the subject's physician, nor the investigator will be informed of the subject's pharmacogenetic results, should they be obtained. If performed, results from individual subjects will be kept confidential and will not be given to anyone not directly involved with this research study. The deoxyribonucleic acid (DNA) samples will be stored by Abbott Laboratories in a secure storage space with adequate measures to protect confidentiality. The DNA samples will be kept by Abbott Laboratories until destroyed by Abbott when this research is completed or the required sample retention time has been satisfied.

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Confidential
ABBT0065831

ABT-594
Protocol M99-114
February 8, 2000

3

6.0 Investigators and Study Administrative Structure

6.1 Investigative Sites

Investigative sites will be selected by Abbott Laboratories. Approximately 30 sites will be selected to enroll subjects for this study.

6.2 Sponsor Information

The sponsor, Abbott Laboratories, will coordinate the activities for initiating this clinical study. The protocol, CRFs and sample informed consent form will be generated by Abbott Laboratories. The database for this study will be created using NOMAD®, a data management system. Designated statisticians at Abbott Laboratories will be responsible for the statistical analysis of the data.

6.3 Contract Research Organization

Abbott Laboratories will delegate prestudy (if necessary) and initiation visits, site monitoring, and post-study site visits to a Contract Research Organization (CRO) for the conduct of this clinical study. The sponsor and CRO will maintain contact in order to manage adequately the progress of the study. The CRO will coordinate and perform all site visits and will prepare trip reports, using the Abbott format, for each visit performed. These reports will detail the activities conducted at all investigative sites and will include all relevant observations. All trip reports will be forwarded to the sponsor in a timely manner to ensure appropriate site management, adhering to Abbott Laboratories Standard Operating Procedures (SOP).

6.4 Clinical Supply Management

Clinical supplies will be prepared by Abbott Laboratories (Investigational Drug Services, D-492) for the study and sent to all investigational sites. Abbott Laboratories will authorize the release of clinical supplies once the appropriate essential documents have been received from the respective site and upon approval by Abbott Laboratories Regulatory Affairs.

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ABBT0065832

ABT-594
Protocol M99-114
February 8, 2000

4

All subjects will be centrally randomized by site and assigned to a treatment group (using a randomization supplied by Abbott Laboratories) using an Interactive Voice Response System (IVRS). The IVRS will be contracted from:

ClinPhone Inc.
29 Emmons Drive, C40
Princeton, NJ 08540

Blinded study medication for each randomized subject (using a randomization supplied by Abbott Laboratories) will also be assigned using IVRS. Each site will keep an accurate inventory of the clinical supplies, including drug shipping and receiving documents, dispensing/accountability records (Appendix E), and records for return of used and unused clinical supplies to Abbott Laboratories. Clinical Research Associates (CRAs) will check drug accountability records regularly.

6.5 Central Laboratory

This study will utilize one central laboratory contracted by, and under the direction of, Abbott Laboratories. All protocol specified clinical laboratory tests will be performed by the following central laboratory:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214

ABT-594
Protocol M99-114
February 8, 2000

5

6.6 Administrative Structure

The administrative structure for this study is depicted in Figure 6.6a.

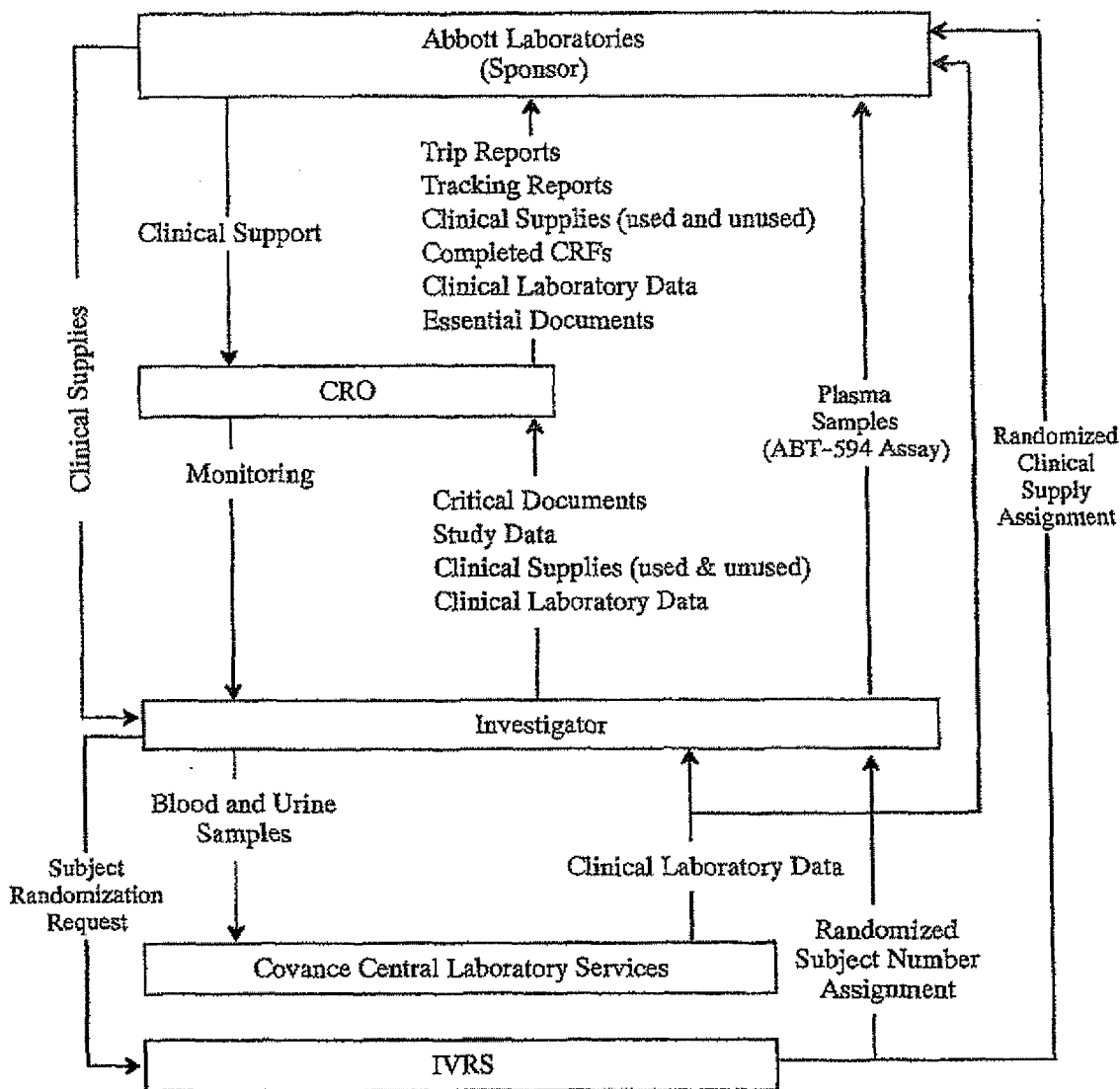


Figure 6.6a Administrative Structure

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Confidential
ABBT0065834

ABT-594
Protocol M99-114
February 8, 2000

6

7.0 Introduction

7.1 Analgesia Today

Pain is one of the most common reasons people consult a physician, representing an extraordinary societal burden. The cost of chronic pain has been estimated to range in the tens of billions of dollars annually.¹

Currently there are four major groups of therapeutics for pain relief: 1) nonsteroidal anti-inflammatory drugs (NSAIDs/COX-2 inhibitors), 2) opioids, 3) adjuvant analgesics (e.g., tricyclic antidepressants [TCAs]), and 4) centrally acting non-narcotic analgesics (e.g., acetaminophen, tramadol). NSAIDs are most often used to treat mild to moderate pain associated with inflammation, but are ineffective in treating some types of nociceptive and neuropathic pain. Risks associated with NSAIDs include gastrointestinal bleeding and hepatic toxicity. COX-2 inhibitors may improve on this gastrointestinal profile, but other adverse events may become evident. Opioids are used for moderate to severe pain. Clinically significant physical dependence and tolerance to analgesia may occur in subjects receiving opioids regularly. In addition, constipation is a significant side effect. Adjuvant analgesics are commonly used for neuropathic pain. Unlike the other groups, the majority of adjuvant analgesics have a delayed onset of an analgesia because of their mechanism of action and the requirement for dose titration. Therefore, a class of compounds with a broad spectrum clinical activity, efficacy in moderate and severe pain, and without the liabilities of opioids, NSAIDs and other currently available analgesics would represent an important advance in pain relief.

7.2 ABT-594

Interest in the potential analgesic activity of compounds acting at neuronal nicotinic acetylcholine receptors (nAChRs) has been enhanced recently by the discovery that (+)-epibatidine, a potent nAChR agonist, is greater than 100-fold more potent than morphine in rodent models of antinociception.² The antinociceptive effects of (+)-epibatidine are blocked by the nAChR antagonist mecamylamine, but not by opioid receptor blockade. Thus, (+)-epibatidine appears to be a potent antinociceptive agent that

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Confidential
ABBT0065835

ABT-594
Protocol M99-114
February 8, 2000

7

acts via activation of neuronal nAChRs and not through opioid receptors. Unfortunately, (\pm)-epibatidine is quite potent at all subtypes of the nAChR (neuronal, ganglionic, and neuromuscular junction) and is quite toxic at antinociceptive doses.³ Because of nAChR diversity, however, it is possible that nAChR ligands with greater receptor subtype selectivity might have therapeutic utility at doses below those associated with side effects.

ABT-594 [(R)-5-(2-azetidylmethoxy)-2-chloropyridine], is a non-opioid, non-NSAID analgesic. It is a novel neuronal nAChR ligand that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 modulates pain transmission by interacting with nAChRs, and not opioid receptors, at key regulatory sites along the pain pathway. It has both peripheral and central antinociceptive effects in preclinical models of acute thermal, persistent chemical, and neuropathic pain states.

To date, only systemic treatment with opioids like morphine has been reported to have this broad spectrum of analgesic activity. Like the opioids, ABT-594 can selectively modulate pain transmission by inhibiting substance P release from C-fibers at the level of the dorsal horn, and by activating the brainstem centers that provide descending inhibitory pathways known to gate painful stimuli. In contrast to morphine, repeated treatment with ABT-594 in pre-clinical studies did not produce withdrawal effects at termination of treatment, suggesting an absence of physical dependence liabilities.

In pre-clinical studies, ABT-594 distributes rapidly to the brain following systemic administration and, like morphine, may work at multiple levels in the central and peripheral nervous systems to modulate pain perception. Compounds like ABT-594 that can selectively modulate neuronal nAChR function and possess broad-based antinociceptive activity may provide a novel therapeutic approach to pain management that avoids the liabilities typically associated with opioid analgesics.

ABT-594
Protocol M99-114
February 8, 2000

8

Human clinical trials with ABT-594 began in 1997. Initial clinical trials were conducted using oral solution formulations. Subsequently, a soft elastic capsule (SEC) formulation and, later, a hard gelatin capsule (HGC) formulation were developed and used in clinical trials.

Phase I clinical trials of the oral solution formulations suggested that 150 µg/day would be the maximally tolerated dose. Subsequent experience in Phase I and II trials with the solid formulations (SEC and HGC), however, has suggested that higher doses would be tolerated. Two Phase I studies with the HGC formulation have recently been completed: Study M99-076 ("A Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, and Pharmacokinetics of Ascending Doses of Twice Daily Dosing Regimens of a Hard Gelatin Capsule Formulation of ABT-594 in Healthy Adult Subjects") and M99-120 ("A Double-Blind, Placebo-Controlled Study of the Safety, Tolerability and Pharmacokinetics of Escalating Doses of Twice Daily Dosing of a Hard Gelatin Capsule Formulation of ABT-594 in Adult Subjects in General Good Health"). Study M99-076 demonstrated that the ABT-594 HGC formulation was generally well tolerated at fixed (untitrated) doses up through 300 µg BID for 14 days. Study M99-120 included titrated doses up through 450 µg BID for 5 days. Adverse events, significantly different than placebo, for subjects receiving 300 µg BID for 14 days in Study M99-076 included: dizziness, nausea, vomiting, asthenia and diarrhea (all of which were considered to be mild in the opinion of the investigator). In addition, results from Study M99-120 suggested that a short period of dose escalation at the initiation of therapy improved tolerability. Throughout Phase I studies of ABT-594, subjects generally tolerated ABT-594 better when dosing followed a meal and after 3-4 days of repeated dosing (the period in which most adverse events occur).

Phase II has included (to date) efficacy and safety studies of ABT-594 in molar extraction, osteoarthritis and neuropathic pain. Based upon a study of molar extraction pain (Study M97-772, "A Randomized, Double-Blind, Single Dose Comparison of an Oral Solution of ABT-594, Ibuprofen, and Placebo in a Post-Surgical Dental Pain Model"), 100 µg ABT-594 (single dose oral solution) appeared to be a minimally efficacious dose in acute pain.

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ABT-594
Protocol M99-114
February 8, 2000

9

A study of ABT-594 in osteoarthritis (Study M98-826, "A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 and Ibuprofen to Placebo in Patients with Pain Associated with Osteoarthritis of the Knee") evaluated the ABT-594 SEC formulation at doses of 25, 50 and 75 µg BID for 3 weeks and a study of ABT-594 in neuropathic pain (Study M98-833, "A Randomized, Double Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Patients with Painful Polyneuropathies") evaluated the same formulation at doses of 25 and 75 µg BID for 3 weeks. Both studies suggested a trend towards analgesic effect at 75 µg BID. In addition, 75 µg BID was generally well tolerated. The most common adverse events (greater than or equal to 5%) for subjects receiving 75 µg BID ABT-594 in the osteoarthritis and neuropathic pain studies (combined) were nausea (15%), headache (13%), dizziness (7%), insomnia (6%) and vomiting (5%). ABT-594 appeared to be tolerated better after the first week of therapy (an effect not related to premature terminations).

Data from Phase I and II studies completed to date suggest that ABT-594 will be generally well tolerated at doses higher than previously studied in Phase II trials (higher than 75 µg BID). In addition, data from Phase II trials suggest that, because a trend toward analgesic efficacy was seen at 75 µg BID, a study of higher doses may demonstrate greater analgesic efficacy. The current study, therefore, will be performed to test this hypothesis.

8.0 Study Objectives

The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy, have an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and have ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert) at the Baseline Visit.

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ABBT0065838

ABT-594
Protocol M99-114
February 8, 2000

10

9.0 Investigational Plan

9.1 Overall Study Design and Plan: Description

This is a Phase II, randomized, double blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who have painful diabetic polyneuropathy. Approximately 320 subjects will be assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg or placebo BID for 49 days on an outpatient basis. Approximately 30 sites will be recruited in order to enroll approximately 320 subjects who meet entry criteria for this study.

The study will be divided into 5 phases: Screening Phase (Day -22 to Day -8), Baseline Pain Assessment Phase (Day -7 to Day -1), Primer Phase (Day 1 to Day 7), Treatment Phase (Day 8 to Day 49) and Post-Treatment Phase (Day 50 to Day 59). Day 1 is the first day of study drug administration. Subjects will be allowed a window of ± 3 days for each study visit. The study design is depicted in Figure 9.1a.

Subjects will review and sign the informed consent prior to the conduct of any study specific procedures. Subjects will then be screened for eligibility by medical history, physical examination, vital sign measurements, and clinical laboratory tests. Those subjects taking tricyclics, serotonin-specific reuptake inhibitors (SSRIs), antiepileptic drugs (AEDs), or other analgesics for the treatment of their pain must have discontinued these drugs at least 7 days prior to the Baseline Pain Assessment Phase (Day -7 to Day -1). During the Baseline Pain Assessment Phase, subjects will complete, at approximately 11 AM each morning, the diary-based Pain Rating Scale (11-Point Likert Scale) of their diabetic polyneuropathy pain intensity. Subjects will not be permitted to take concomitant analgesics, except for limited doses of acetaminophen (as specified in Section 9.4.7) during the Baseline Pain Assessment Phase.

On the day after the Baseline Pain Assessment Phase, subjects will return to the site for their Baseline Visit (Day 1). At this visit, diaries will be collected and reviewed. In addition, subjects will complete the site-based Pain Rating Scale (11-Point Likert Scale). Subjects who meet all entry criteria, including an average of ≥ 4 points on the

ABT-594
Protocol M99-114
February 8, 2000

11

diary-based Pain Rating Scale (11-Point Likert) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Visit, will then complete the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute). Subjects will undergo an interim medical history, physical examination, vital sign measurements, ECG and clinical laboratory tests.

Subjects who meet all entry criteria at the Baseline Visit will be randomly assigned in an equal ratio into 1 of 4 treatment groups: ABT-594 150 µg BID, ABT-594 225 µg BID, ABT-594 300 µg BID, or placebo. Subjects will start study drug at the evening dose on Day 1 (as specified in Section 9.4.5). During the Primer Phase, subjects randomized to ABT-594 will receive a fixed dose escalation of ABT-594 (as specified in Section 9.4.1). Following the Primer Phase, subjects will enter the Treatment Phase (Day 8) and will continue their treatment for a total of 49 days. During the Primer and Treatment Phases, subjects will not be permitted to take concomitant analgesics, except for limited doses of acetaminophen (as specified in Section 9.4.7)

Subjects will complete the diary-based Pain Rating Scale each morning (approximately 11 AM), 3 hours after taking their morning dose of study drug. They will return to the site for study procedures on Day 14 (Treatment Visit I), Day 21 (Treatment Visit II) and Day 35 (Treatment Visit III) and Day 49 (Treatment Visit IV). Procedures during Treatment Visits I, II, III, and IV will include collection of diaries (and issuance of the next set of diaries at Treatment Visits I, II and III) and efficacy and safety assessments: the site-based Pain Rating Scale, the Neuropathic Pain Scale, the Subject and Clinician Global Impression of Change (Treatment Visit IV only), the SF-36™ Health Status Survey (Acute) (Treatment Visit IV only), physical examination (Treatment Visit IV only), vital sign measurements and clinical laboratory tests (Treatment Visits I, III and IV), ABT-594 plasma assay collection (Treatment Visits I and IV only) and ECG (Treatment Visit IV only). A subset of subjects at selected sites will undergo intensive pharmacokinetic sampling at Treatment Visits I and IV.

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ABBT0065840

ABT-594
Protocol M99-114
February 8, 2000

12

On the day after Treatment Visit IV, subjects will enter the Post-Treatment Phase. Subjects will no longer take study drug or complete pain scales. Subjects may restart all discontinued medications under the guidance of their physician. Subjects will return for study procedures at the Follow-up Visit (7 to 10 days after their final study drug dose). Procedures at the Follow-up Visit will include physical examination, vital sign measurements, recording of any adverse events since Treatment Visit IV and re-examination of any abnormal ECG or clinical laboratory findings present at the previous evaluation.

For those subjects who participate in clinical studies of ABT-594 and who consent, a blood sample will be collected at Treatment Visit I in order to obtain a sample of genetic material (DNA). The DNA sample may be used at a later date to investigate associations between genetic differences (polymorphisms) and differences in the way subjects respond to treatment, in terms of efficacy or side-effects or both. If a genetic factor in response is identified, it may allow the development of a diagnostic test to identify those most likely to benefit before actually taking the drug. The sample may also be used to identify genes involved in painful diabetic polyneuropathy.

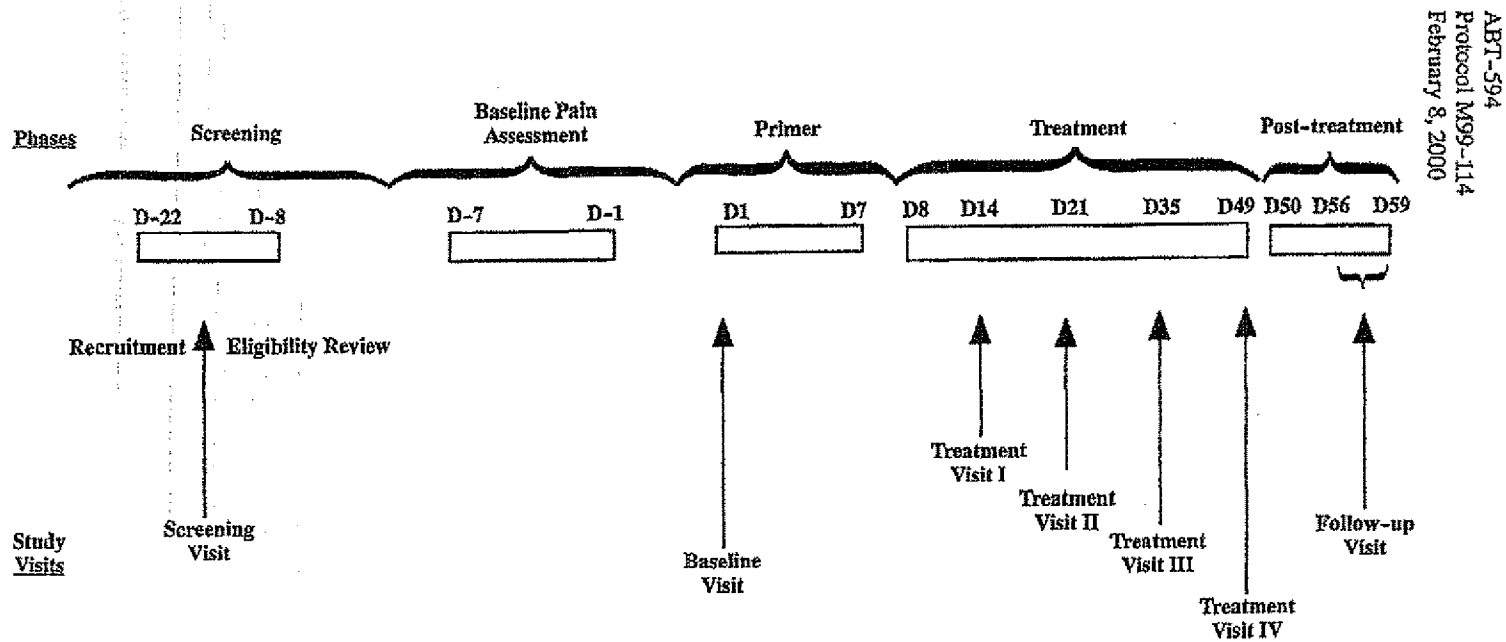


Figure 9.1a Study Schematic

ABT-594
Protocol M99-114
February 8, 2000

14

9.2 Discussion of Study Design, Including the Choice of Control Groups

The design of this study provides a placebo control group to assess the analgesic efficacy of ABT-594. Double-blind, parallel group designs are generally acknowledged as standard for unbiased estimates of treatment group differences. Validated pain scales will be employed.

9.3 Selection of Study Population

It is anticipated that approximately 320 subjects will be randomized and receive study medication in this study. A subject may be randomized in this study provided that he/she meets all of the inclusion criteria outlined in Section 9.3.1 and does not meet any of the exclusion criteria in Section 9.3.2.

9.3.1 Inclusion Criteria

9.3.1.1 Prior to any study specific procedure, voluntary written informed consent must be obtained from the subject after the purpose and nature of the study have been explained.

9.3.1.2 The subject must be age 18 or older and in relatively good health with a recent stable medical history.

9.3.1.3 The subject's weight must be ≤ 265 pounds.

9.3.1.4 A female subject must be non-lactating and:

- of non-childbearing potential (either postmenopausal for at least 1 year or surgically sterile, including tubal ligation),

OR

- of childbearing potential using oral or barrier contraceptive methods for at least 2 months preceding randomization (and must continue contraceptive method through the course of the study).

All female subjects must have a negative β subunit human chorionic gonadotropin (β -hCG) at the Baseline Visit. Female subjects of childbearing potential must have a negative β -hCG at all Treatment Visits.

ABT-594
Protocol M99-114
February 8, 2000

15

- 9.3.1.5 The subject must have a diagnosis of diabetes mellitus (Type I or Type II) and a diagnosis of distal symmetric diabetic polyneuropathy.
- 9.3.1.6 The subject must have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy.
- 9.3.1.7 The location and quality of the pain under study are consistent with distal symmetric diabetic polyneuropathy in the opinion of the investigator.
- 9.3.1.8 The subject has distal symmetric diabetic polyneuropathy symptoms (including pain) which have been stable for at least the last 3 months prior to the Screening Visit (defined by the opinion of the investigator).
- 9.3.1.9 The subject must have an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-point Likert Scale) at the Baseline Visit.

9.3.2 Exclusion Criteria

- 9.3.2.1 The subject has positive test results for drugs of abuse or viral hepatitis at the Screening Visit, or has a known history of a positive test result for HIV.
- 9.3.2.2 The subject has recent (< 5 years) history of drug or alcohol abuse or dependence.
- 9.3.2.3 The subject has an acute or chronic renal or hepatic disorder, psychiatric disease or disorder or any uncontrolled medical illness.
- 9.3.2.4 The subject has active malignancy of any type or a history of malignancy (excluding basal cell carcinoma that has been treated or other malignancies that have been surgically removed and have had no evidence of recurrence for a minimum of 5 years prior to study start).
- 9.3.2.5 The subject has taken an investigational drug within 1 month prior to administration of study treatment or is scheduled to receive an investigational drug other than ABT-594 during the course of this study.

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ABBT0065844

ABT-594
Protocol M99-114
February 8, 2000

16

- 9.3.2.6 The subject has a diastolic blood pressure greater than 95 mm Hg and/or a systolic blood pressure greater than 170 mm Hg (sitting) at the Screening Visit.
- 9.3.2.7 The subject has orthostatic hypotension at the Screening Visit (as defined as a decrease in systolic blood pressure of at least 20 mm Hg or 10 mm Hg in diastolic blood pressure from supine to standing sustained after 1 minute of standing), or a history of syncope or pre-syncope symptoms.
- 9.3.2.8 The subject has previously participated in a study involving ABT-594, including the present study.
- 9.3.2.9 The subject has clinically significant abnormalities in clinical chemistry, hematology, or urinalysis, including AST or ALT ≥ 1.5 times the upper limit of the reference range or a serum creatinine > 1.5 mg/dL. Subjects may have elevated serum and urine glucose, but their serum glucose must have been under good control (in the opinion of the investigator) for at least the last 3 months prior to the Screening visit.
- 9.3.2.10 The subject has clinically significant electrocardiographic abnormalities.
- 9.3.2.11 The subject has ongoing treatment with or expected treatment with any medication not allowed as described in Section 9.4.7, including at least 7 days prior to the Baseline Pain Assessment Phase.
- 9.3.2.12 The subject has a diagnosis of fibromyalgia, arthritis, bursitis, tendinitis, vascular disease or other painful disorders affecting the extremities (other than the neuropathy under study) that the subject cannot differentiate from the neuropathy pain.
- 9.3.2.13 The subject has sympathetically maintained pain (e.g., Reflex Sympathetic Dystrophy, Causalgia), defined by the opinion of the investigator.
- 9.3.2.14 The subject is unlikely to comply with the study protocol or is unsuitable for any other reason, in the opinion of the investigator.

9.3.3 Removal of Subjects from Therapy

A subject may voluntarily terminate participation in the study at any time. The investigator may also decide, for medical reasons or protocol noncompliance, to

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ABBT0065845

ABT-594
Protocol M99-114
February 8, 2000

17

terminate prematurely a subject's participation. The investigator must notify the CRA within 24 hours and document the reason for premature termination on the appropriate CRF.

Subjects, whose participation is terminated prematurely after signing study consent but before study drug administration, will not require follow-up observations. Subjects, whose participation is terminated prematurely after study drug administration must undergo procedures normally performed at Treatment Visit IV (see Table 9.5a) within 7-10 days following termination from the study.

If, in the judgment of Abbott Laboratories and possibly in consultation with the investigators, continued exposure to a study drug represents a significant risk to subjects, the study will be terminated.

9.4 Treatments

9.4.1 Treatments Administered

Subjects will be randomly assigned in an equal ratio to 1 of the following 4 treatment groups:

ABT-594 150 µg BID
ABT-594 225 µg BID
ABT-594 300 µg BID
Placebo for ABT-594 BID

ABT-594 and matching placebo will be supplied as Light Gray Opaque No. 1 HGCs.

During the Primer Phase, subjects will receive a fixed dose escalation of ABT-594. ABT-594 will be initiated at 75 µg BID. The dose will increase every 2 days in 75 µg BID increments until subject are taking their assigned treatment dose (150, 225 or 300 µg BID). The ABT-594 dose escalation scheme is presented in Table 9.4.1a.

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ABBT0065846

ABT-594
Protocol M99-114
February 8, 2000

18

Table 9.4.1a ABT-594 Dose Escalation

Treatment Regimen	Suggested Dosing Time	Days 1-7							Day 8
		1	2	3	4	5	6	7	8
150 µg ABT-594	8 AM		75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
225 µg ABT-594	8 AM		75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
300 µg ABT-594	8 AM		75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg
	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg

Subjects will start study drug at PM dose on Day 1 (Section 9.4.5).

The number and type of HGCs per dose for the Treatment Phase is presented in Table 9.4.1b.

Table 9.4.1b Number and Type of Capsules by Treatment Regimen

Treatment Regimen	Number of Capsules Per Dose (Days 8-49)	
	Daily Blister Card (BID doses)	
	75 µg ABT-594 HGC	Placebo ABT-594 HGC
ABT-594 150 µg	2	2
ABT-594 225 µg	3	1
ABT-594 300 µg	4	0
Placebo	0	4

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ABBT0065847

ABT-594
Protocol M99-114
February 8, 2000

19

9.4.2 Identity of Investigational Products

Table 9.4.2a Identity of Investigational Products

Test Preparation Drug Product	Drug Product Lot #	Drug Substance Lot #	Source
ABT-594 75 µg HGC Formulation A-2	58-293-AR	52-015-KD-00	Abbott ¹
Placebo HGC No. 1, Light Gray Opaque (Starch)	55-243-AR-01	N/A	Abbott ¹

¹ Pilot Plant, North Chicago, Illinois

ABT-594 75 µg HGC and placebo HGC are identical in appearance, encapsulated in Light Gray Opaque capsule size No. 1 HGCs.

9.4.2.1 Packaging and Labeling

Study drug supplies will be blinded and packaged in blister cards in accordance with a randomization schedule supplied by Abbott Laboratories (Department of Clinical Statistics). Daily study medication cards will be provided to each subject.

Daily study medication cards will be labeled with the Module Number (assigned by Abbott, via IVRS), New Product Research Order (NPRO) number, Abbott address, study number, contents, storage conditions and directions for use.

Space will be provided on the label of each carton containing the daily study medication cards to record the subject initials and subject randomization number.

9.4.2.2 Storage and Disposition of Supplies

All clinical supplies must be stored in a secure location until dispensed to a subject or until returned to Abbott Laboratories. All blinded study drug supplies must be stored at controlled room temperature (68-77°F, see USP).

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Confidential
ABBT0065848

ABT-594
Protocol M99-114
February 8, 2000

20

9.4.2.3 Drug Accountability

The investigator or designee will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Clinical Supplies Invoice (CSI) or similar document. Study drug will be dispensed after randomization and assignment of study medication by IVRS (Section 9.4.3) for each subject who meets the enrollment criteria. The investigator or designee will record the subject number, subject initials and date dispensed to the subject on the Drug Accountability Form (Appendix E). The amount of study drug remaining will be recorded at Visits I, II, III and IV for each subject on the site Drug Accountability Form. An accurate running inventory of study drug will be kept and will include the NPRO number, CSI number(s), the number of modules dispensed and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the CRA throughout the study and at the site close-out visit. All used and unused supplies must be inventoried, accounted for and returned to Abbott Laboratories. A copy of the Drug Accountability Form, in accordance with the instructions of the CRA, will also be included in the shipment. The investigator agrees not to supply study medication to any persons not enrolled in the study or not named as a subinvestigator on FDA Form 1572.

9.4.3 Method of Assigning Subjects to Treatment Groups

The randomization schedule will be computer-generated before the start of the study by Abbott Laboratories Department of Clinical Statistics. All subjects will be centrally randomized by investigative site using an Interactive Voice Response System (IVRS). Before the study is initiated, the telephone number and call-in directions for the IVRS will be provided to each site.

Approximately 320 subjects will be randomized in an equal ratio to receive either ABT-594 150 µg BID, ABT-594 225 µg BID, ABT-594 300 µg BID or placebo. Subjects will be assigned randomization numbers in ascending numerical sequence per investigative site at the Baseline Visit.

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ABBT0065849

ABT-594
Protocol M99-114
February 8, 2000

21

9.4.4 Selection of Doses in the Study

ABT-594 doses (150 µg, 225 µg, and 300 µg BID) were selected on the basis of Phase I and Phase II studies, and represent doses below the maximally tolerated dose. Phase II data suggested that ABT-594 doses greater than 75 µg BID may be efficacious in the relief of osteoarthritis and distal symmetrical neuropathy pain.

The selection of BID dosing for ABT-594 was based upon Phase I pharmacokinetic results. ABT-594 doses for the Primer Phase (75 µg, 150 µg, and 225 µg BID) were selected based on Phase I safety and pharmacokinetic data.

9.4.5 Selection and Timing of Dose for Each Subject

During the Primer Phase, subjects will start study drug at the evening dose on Day 1 within 1 hour following a meal (e.g., 8 PM). Subjects will then take BID doses of ABT-594 (75 µg, 150 µg, 225 µg or placebo during the Primer Phase and ABT-594 150 µg, 225 µg, 300 µg or placebo during the Treatment Phase) within 1 hour following a meal (e.g., at 8 AM and 8 PM).

Study drugs should be taken with at least one cup (8 ounces) of water.

9.4.6 Blinding

Both the investigator and the subject will remain blinded to the subject's treatment throughout the course of the study. The study blind may be broken if, in the opinion of the investigator, it is in the subject's best interest to know the study drug assignment. The sponsor (Abbott Laboratories) **MUST** be notified before breaking the blind unless identification of the study drug is required for emergency therapeutic measures. Blind breaking information will be provided using IVRS. Before the study is initiated, the telephone number and call-in directions for the IVRS will be provided to each site. The sponsor must then be notified within 48 hours of the blind being broken. The date, and reason for blind breakage must be recorded on the appropriate CRF.

9.4.7 Prior and Concomitant Therapy

At the Screening Visit, a history of medications used over the prior 2 weeks will be taken.

ABT-594
Protocol M99-114
February 8, 2000

22

Concomitant analgesics (prescription or over-the-counter [OTC] except aspirin and acetaminophen as described below), including serotonin-specific reuptake inhibitors, tricyclic antidepressants, antiepileptic medications, sodium channel blockers (e.g., mexilitine), opioids, capsaicin, non-steroidal anti-inflammatory drugs, COX-2 inhibitors, muscle relaxants, TENS and topical analgesics will not be allowed.

Aspirin, 325 mg daily maximum, is permitted if taken for primary prevention of thromboembolic events and the dose has been stable for ≥ 1 month prior to the Baseline Visit. Acetaminophen, 3 grams daily maximum, or 6 grams maximum during the Baseline Pain Assessment Phase and per week, for each of the 7 weeks of the Primer and Treatment Phases, is permitted. Subjects will not be allowed to take analgesic medication (including acetaminophen) within 24 hours of the Baseline Visit and Treatment Visits I, II, III and IV.

If the administration of any concomitant medication is necessary during the course of this study, the medication name, dosage information, frequency and dates of administration must be reported on the CRF. Concomitant analgesic medication use (frequency only) will be recorded separately on the Concomitant Analgesic Medication Use CRF at the Baseline Visit and Treatment Visits I, II, III and IV. The concomitant medication use record will include the number of separate occasions each subject has used protocol-allowed (limited amounts) acetaminophen and any other analgesic (taken as a protocol violation) since the subject's previous visit.

9.4.8 Treatment Compliance

In order to document compliance with the treatment regimen, subjects will be instructed to return all medication cards and cartons (even if empty) to the study coordinator at Treatment Visits I, II, III and IV. Treatment compliance will be documented by the investigator or designee on the site Drug Accountability Form (Appendix E) and on the appropriate CRF.

Overdose information will be collected on the appropriate CRF.

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ABBT0065851

ABT-594
Protocol M99-114
February 8, 2000

23

9.5 Efficacy, Pharmacokinetic and Safety Variables and Other Study Procedures

9.5.1 Efficacy and Safety Measurements Assessed and Flow Charts

Study procedures will be performed as summarized in Table 9.5a., Study Procedures Flow Chart.

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Table 9.5a Study Procedures Flow Chart

Study Activity	Screening Phase D-22 and D-8	Baseline Pain Assessment Phase D-7 to D-1	Primer Phase D1-D7		Treatment Phase D8-D49				Post-Treatment Phase D50-D59	
	Screening Visit		Baseline Visit D1	D2-D7	D8- D49	Treatment Visit				Follow-up Visit D56 to D59
						D14 I	D21 II	D35 III	D49 IV ^a	
Informed Consent	X									
Medical History	X		X ^b							
Physical Exam	X ^c		X						X	X
Vital Signs	X ^d		X ^e			X		X	X	X
ECG			X						X	X ^f
Clinical Laboratory Tests ^g	X		X			X		X	X	X ^f
Viral Hepatitis Screen	X									
Urine Drug and Alcohol Screen	X									
Pregnancy Test			X			X ^h	X ^h	X ^h	X ^h	
Genetic Polymorphism Sample (If Applicable)			X							
ABT-594 Plasma Assay						X			X	
ABT-594 PK Profile ⁱ						X			X	
Diary Issued	X		X			X	X	X		
Diary Collected			X			X	X	X	X	
Diary-Based Pain Rating Scale ^j		X		X	X					
Site-Based Pain Rating Scale			X			X	X	X	X	
Neuropathic Pain Scale			X			X	X	X	X	
Subject/Clinician Global Impression of Change									X	
SF-36 [™]			X						X	
Randomize Patient			X							
Dispense Study Drug			X			X ^k	X	X		
Analgesic Use Monitoring			X			X	X	X	X	
Adverse Event Monitoring			X			X	X	X	X	X
Concomitant Medication Monitoring			X			X	X	X	X	X
Study Drug Accountability		X				X	X	X	X	

^a Or upon premature termination.^b Interim history.^c Includes height.^d Includes orthostatic measurements at Screening Visit only.^e Includes oral temperature at Baseline Visit only.^f Performed only if there are clinically significant abnormalities at the previous evaluation.^g Chemistry, hematology and urinalysis.^h Required of all females of child-bearing potential.ⁱ Study drug must be taken in front of study staff. Blood samples from selected subjects will be taken just prior to dosing (0 hour), and at 1.5, 3, 5, and 8 hours after dosing at selected sites only.^j To be completed at approximately 11 a.m. each morning during the Baseline Pain Assessment Phase and approximately 3 hours after the morning dose during the Primer and Treatment Phases.^k Redispense D15-20 study medication after checking drug accountability.

ABT-594
Protocol M99-114
February 8, 2000

ABT-594
Protocol M99-114
February 8, 2000

25

9.5.1.1 Efficacy Measurements

Prior to any efficacy measurements, a trained site observer will instruct the subject on how to perform and record all pain assessments.

The baseline for all efficacy measurements (except for the diary-based Pain Rating Scale) will be the last evaluation performed prior to receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale will be the average of the last 7 pain scores prior to Day 1 of the study.

Efficacy assessments include the diary-based and site-based Pain Rating Scale (11-Point Likert Scale), the Neuropathic Pain Scale and the Subject Global Impression of Change, Clinician Global Impression of Change, and SF-36™ Health Status Survey (Acute).

Efficacy measurements should be performed (when possible) 3-4 hours post dose.

Pain Rating Scale (11-Point Likert Scale)

Subjects will assess pain intensity daily by completing the Pain Rating Scale (Appendix F) in their diaries. These assessments will be completed daily at approximately the same time each morning (approximately 11 AM) during the Baseline Pain Assessment Phase and daily at the same time each morning (approximately 3 hours after the morning dose of study medication) during the Primer and Treatment phases. Subjects will record the time they completed these assessments in their diaries.

Subjects will also assess pain intensity by completing the Pain Rating Scale at the Investigative Site. These assessments will be completed at the Baseline Visit and at Treatment Visits I, II, III, and IV (or upon premature termination). The time of assessment will be recorded on the appropriate CRF.

Neuropathic Pain Scale

The Neuropathic Pain Scale (Appendix G) will be completed by subjects at the Baseline Visit and at Visits I, II, III, and IV (or upon premature termination).

ABT-594
Protocol M99-114
February 8, 2000

26

Subject Global Impression of Change

The Subject Global Impression of Change (Appendix H) of analgesic relief due to study drug will be performed at Treatment Visit IV (or upon premature termination).

Clinician Global Impression of Change

The Clinician Global Impression of Change (Appendix H) of a subject's analgesic relief due to study drug will be performed at Treatment Visit IV (or upon premature termination).

SF-36™ Health Status Survey (Acute)

The SF-36™ Health Status Survey (Acute) will be completed by each subject at the Baseline Visit and at Treatment IV (or upon premature termination).

9.5.1.2 Safety Measurements and Procedures

Informed Consent

The investigator or designated representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject and by the person who administered the informed consent. A copy of the informed consent form will be given to the subject and a copy will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study related procedures and that the subject received a signed copy.

Medical History

A complete medical history will be obtained from each subject during the Screening Visit. In addition, history of tobacco and alcohol use, and medication (prescription or OTC) use over the 2 weeks prior to screening will be recorded. The medical history will be updated at the Baseline Visit.

ABT-594
Protocol M99-114
February 8, 2000

27

Physical Examination

A physical examination, including weight, will be performed at the Screening Visit, Baseline Visit, Treatment Visit IV and at the Follow-up Visit. Height will be measured at the Baseline Visit only. The physical examination performed at the Baseline Visit will serve as the baseline physical examination.

Vital Signs

Blood pressure, pulse rate and respiration rate will be measured at the Screening Visit, Baseline Visit, Visits I, III, and IV and at the Follow-up Visit. Orthostatic blood pressure and pulse rate will be measured at the Screening Visit only. Oral temperature will be taken at the Baseline Visit only. Vital sign measurements at the Baseline Visit will serve as the baseline vital sign measurements.

Protocol-specified blood pressure and heart rate measurements (except orthostatic) should be obtained after the subject has been sitting for at least 3 minutes. Orthostatic measurements should be obtained after 3 minutes in the supine position and then after 1 minute in the standing position. A cuff of suitable size should be applied evenly and firmly to the exposed upper arm. Subjects should not wear tight sleeves. Ideally, the subject's blood pressure should be measured in the same arm by the same study personnel using the same instrument.

Blood pressure and heart rate measurement should precede, not follow, scheduled blood draws. Subjects should be kept as calm and undisturbed as possible during blood pressure and heart rate measurements.

Electrocardiogram (ECG)

A resting 12-lead ECG will be obtained at the Baseline Visit and Treatment Visit IV. An ECG will be performed at the Follow-up Visit only if clinically significant abnormalities are present on the previous evaluation. The ECG performed at the Baseline Visit will serve as the baseline ECG.

A qualified physician will interpret the ECG. One copy of each 12-lead ECG and physician's report will be retrieved by the CRA with the CRF.

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ABT-594
Protocol M99-114
February 8, 2000

28

Clinical Laboratory Testing

Samples will be obtained for the laboratory tests listed in Table 9.5.b at the Screening Visit, Baseline Visit (Day 1), and Treatment Visits I, III, and IV. Laboratory tests will be obtained at the Follow-up Visit only if clinically significant abnormalities are present on the previous evaluation. The laboratory test results obtained at the Baseline Visit will serve as the baseline results. Blood draws should be performed after pain assessments or vital sign determinations during a visit.

Table 9.5b Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	BUN	Specific gravity
Hemoglobin	Creatinine	Ketones
Red Blood Cell (RBC) count	Total bilirubin	pH
White Blood Cell (WBC) count	Alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT)	Bilirubin
Neutrophils	Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT)	Protein
Monocytes	Lactate Dehydrogenase (LDH)	Blood
Bands	Alkaline phosphatase	Glucose
Basophils	Sodium	Microscopic evaluation
Eosinophils	Potassium	
Hemoglobin A _{1c} (Baseline Visit Only)	Chloride	
Lymphocytes	Calcium	
Mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH)	Inorganic phosphorus	
Platelet count (estimate not acceptable)	Uric Acid	
Prothrombin Time (PT)	Bicarbonate	
Partial Thromboplastin Time (PTT)	Cholesterol	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin	

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests.

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ABT-594
Protocol M99-114
February 8, 2000

29

The investigator will review all laboratory test results and will assess clinical significance for each abnormal result. All laboratory test results that are considered clinically significant by the investigator will be followed to a satisfactory resolution.

A copy of each laboratory report must be included with the CRF.

Viral Hepatitis Screen

Subjects will undergo serological evaluation for viral hepatitis (hepatitis A virus IgM antibody, hepatitis B virus surface antigen, and hepatitis C virus antibody) at the Screening Visit. The hepatitis test panel will be performed by the central laboratory.

Urine Drug Screen and Alcohol Screen

Urine specimens will be tested for drugs of abuse and alcohol at the Screening Visit and will be performed by the central laboratory.

Pregnancy Test

A urine pregnancy test will be performed by designated study personnel at the Baseline Visit for all female subjects and at Visits I, II, III, and IV for female subjects of childbearing potential. A lactating or pregnant female will not be eligible for participation in this study.

Adverse Events

An adverse event is defined as any unexpected and unfavorable event such as a disease, syndrome, sign, symptom, and/or laboratory finding associated temporally with the use of a drug in humans, whether or not thought to be drug-related and whether observed by the investigator or reported by the subject.

The subject will be instructed to contact the investigator if an adverse event occurs so that appropriate action can be taken and all adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject, will be reported on the appropriate CRF.

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ABBT0065858

ABT-594
Protocol M99-114
February 8, 2000

30

The investigator will assess and record any adverse event in detail on the adverse event CRF including the date of onset, description, final diagnosis (if known), severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for the event, and action taken. For adverse events to be considered as sporadic, the events must be of similar nature and severity.

The investigator will use the following definitions to rate the severity of each adverse event:

Table 9.5c Definitions for Investigator Rating of Adverse Event Severity

Rating	Definition
Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

ABT-594
Protocol M99-114
February 8, 2000

31

Table 9.5d Definitions for Investigator Assessment of Adverse Event Relationship to Study Drug

Rating	Definition
Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on rechallenge and another etiology is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology).

If an investigator opinion of possibly, probably not, or not related to study drug is given, an alternate etiology must be provided for the adverse event.

Adverse events will be monitored continuously from the time of study drug administration to the Follow-up Visit. In addition, adverse events spontaneously reported to the investigator after completion of the Treatment Phase (or after premature termination) will be collected up to 30 days after drug discontinuation and reported to Abbott Laboratories. Subjects will be instructed to report to the investigator any other adverse events that occur after Follow-up Visit.

Serious adverse events, as well as adverse events that the investigator considered to be related to study design and/or procedures that occur after signing the Informed Consent and prior to the first dose of study drug will also be collected.

Any abnormal laboratory value or change in vital signs will not be documented as an adverse event unless it is a reason for premature discontinuation from the study, requires treatment, or meets regulatory criteria for a serious adverse event.

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ABBT0065860

ABT-594
Protocol M99-114
February 8, 2000

32

Ongoing medical conditions will be considered adverse events if there is an increase in severity or frequency of occurrence. Since measurements of pain intensity are efficacy measurements in this study, an increase in severity or frequency of occurrence of the pain under study will not be considered adverse events for the purposes of this study.

Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to Abbott Laboratories as a serious adverse event (SAE) within 24 hours of occurrence or notification to the site:

Death of Subject:	An event which results in the death of a subject.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in fatality if immediate medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an admission to the emergency room or outpatient facility.
Prolongation of Hospitalization:	An event which occurs while the study subject is hospitalized and that prolongs the subject's hospital stay.
Persistent or Significant Disability/Incapacity:	An event which results in a condition that interferes with the activities of daily living of a study subject (e.g., permanent loss of vision).

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ABBT0065861

ABT-594
Protocol M99-114
February 8, 2000

33

Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that, based on medical judgement, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed in the "serious" definition (e.g., allergic bronchospasm requiring intensive treatment in the home or emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

In addition, miscarriage/spontaneous and elective abortions will be reported to Abbott Laboratories as serious adverse events.

In the event of a serious adverse event, whether related to study drug or not, the investigator and other professional personnel in attendance will be notified as soon as possible for the appropriate action. The investigators will notify by telephone, one of the following people at Abbott Laboratories within 24 hours of being made aware of any serious adverse event.

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ABT-594
Protocol M99-114
February 8, 2000

34

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In addition, a written confirmation of the occurrence, including any supplementary data, must be sent within 3 days of the telephone report to:

Bruce G. McCarthy, M.D.
Dept. 48Q, Bldg. AP34
Abbott Laboratories
200 Abbott Park Road
Abbott Park, IL 60064-6193
Fax: (847) 938-5258

9.5.2 Appropriateness of Measurements

All efficacy measurements in this study are validated and are considered standard for this population. All clinical and laboratory procedures in this study are standard and generally accepted.

9.5.3 Efficacy Variables

All efficacy variables will be derived from the efficacy measurements (Section 9.5.1.1).

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ABBT0065863

ABT-594
Protocol M99-114
February 8, 2000

35

9.5.3.1 Primary Variable(s)

The primary efficacy measurement will be the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. The baseline pain score for the diary data is defined as the average of the last 7 pain scores prior to receiving the first dose of blinded study drug on Day 1 of the study.

9.5.3.2 Secondary Variable(s)

Change from baseline to final and each scheduled evaluation will be calculated for each of the following secondary efficacy variables:

- Diary-based Pain Rating Scale (11-Point Likert), change from baseline to each evaluation only
- Site Based Pain Rating Scale (11-Point Likert)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health]⁴ PCS, and MCS.⁵

The pain evaluations recorded at the Baseline Visit will be used as the baseline score for pain evaluations assessed at the investigative site.

9.5.4 Drug Concentration Measurements

9.5.4.1 Collection, Processing and Storage of Blood Samples for ABT-594 Plasma Assay

Blood samples for ABT-594 plasma assay will be collected from all subjects at Treatment Visits I and IV. One blood sample (approximately 7 mL) will be collected into a sodium heparin evacuated collection tube at each visit. Blood draws should be

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Confidential
ABBT0065864

ABT-594
Protocol M99-114
February 8, 2000

36

performed after any pain assessments or vital sign determinations during a visit. For subjects who prematurely discontinue, a blood sample will be taken for ABT-594 assay at the premature discontinuation visit, and the exact times at which the dose was taken will be recorded.

All blood samples will be immediately stored at 4°C or below. The samples will be separated by centrifugation within one hour after sample collection. The supernatant will be transferred by polypropylene pipettes into plastic vials clearly marked as "Assay Plasma" and labeled with the study drug number, protocol number, subject number, initials, and date and time of sample collection. This information will also be recorded on the appropriate CRF. All labeled plastic vials will be placed in a rack to prevent breakage. **Plasma samples for determination of ABT-594 must be frozen at -5°C or colder within one hour from centrifugation.** All specimens will be kept frozen at -5°C or colder until packed in solid carbon dioxide (dry ice) for shipment to Abbott Laboratories.

The time and date of each subject's morning dose on the day of plasma assay blood draw, the time and date of the meal eaten prior to the morning dose, and the time and date of the evening dose on the day prior to the plasma assay blood draw will be recorded in the CRF.

9.5.4.2 Additional Pharmacokinetic Sampling

For those subjects participating in the additional pharmacokinetic sampling for PK profile (approximately 30 subjects), blood samples will be collected at Treatment Visits I and IV.

After establishing the time of the Treatment Visit, the subject will be instructed to take the preceding day's study drug as close as possible to 8 PM. At the office visit, the study medication will be taken in the presence of the office staff in order to allow proper and accurate recording of blood collection times relative to dosing. The time of the visit should accommodate a target time for the morning dose of 12 hours after the preceding evening's dose. Blood samples will be collected as follows: just prior to dosing (0 hour)

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Confidential
ABBT0065865

ABT-594
Protocol M99-114
February 8, 2000

37

and at 1.5, 3, 5, and 8 hours after the morning dosing. Subjects will receive their 8 PM dose as scheduled. Subjects will be confined at the site until the blood sample at the 8 hour time point is collected. Pharmacokinetic profile samples will be processed and stored as specified in Section 9.5.4.1 until shipment to Abbott Laboratories.

9.5.4.3 Shipment of Plasma Samples

An inventory list of the samples included in the shipment must accompany the shipment. The inventory list will include the shipping date, number of samples in the container, drug identification, Abbott protocol number, subject numbers, sample type, sampling times, and missing samples. The frozen samples will be packed in dry ice sufficient to last 2 days during shipping.

Arrangements will be made with Abbott Laboratories for shipping of the plasma samples to the following Abbott address:

Sample Receiving
Abbott Laboratories
Dept. 4TA, Bldg. AP9
100 Abbott Park Road
Abbott Park, IL 60064-6122
Phone: (847) 937-0889
Fax: (847) 938-9898

On the day of shipping, a copy of the inventory sheet should be faxed to the Sample Receiving Department at (847) 938-9898.

9.5.5 Blood Samples for Genetic Polymorphism Analysis

Two 10 mL whole blood samples will be collected in purple top (EDTA) tubes at the Baseline Visit and shipped immediately at ambient or refrigerated temperature to:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214

If clear differences in response are noted during the clinical development of ABT-594 and believed to be genetically related, these samples may be analyzed as part of a multicenter, multistudy project to identify genetic factors involved in the response to

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Confidential
ABBT0065866

ABT-594
Protocol M99-114
February 8, 2000

38

ABT-594 or drugs of this class. The specific response may be related to efficacy or safety, or both. The results of this potential analysis will not be reported with the study summary. The samples may also be used for development of a diagnostic test for drug response.

The pharmacogenetic analyses involve two methods: one which examines known genes believed to be involved in the particular response (Candidate Gene), and one which uses a high density marker map to locate and identify genes related to the response (Genomic Association) by comparing the marker profile between the subjects with an effect and a corresponding negative control group. The Candidate Gene method includes genes related to drug metabolism, drug targets or target pathways, and others including genes relating to cellular homeostasis. The Genomic Association method utilizes a map of single nucleotide polymorphisms which by themselves are essentially meaningless, but when correlated with groups of two distinct subject groups allow the identification of the gene(s) related to the difference between the groups. For the purpose of pharmacogenetic studies such as this, the difference would be related to the response to the drug or the presence or absence of the disease being tested.

9.6 Data Quality Assurance

Prior to the initiation of this protocol, an investigator's meeting will be held with Abbott personnel, the investigators and their study coordinators, the CRO's project manager and CRAs. This meeting will entail a detailed discussion of the protocol, CRF completion, and specimen collection methods. In addition to the investigator's meeting, the study personnel at each site will be trained on the study procedures by a CRA at a study initiation visit and be given a CRF completion workbook for reference. The CRAs will monitor each site approximately every 4 weeks. At each visit, 100% source-document review will be made against the entries on the CRFs and a quality-assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. The investigator must agree to provide Abbott Laboratories (or designee) access to all source documents in order to verify CRF entries. In addition, after CRFs are retrieved by the CRA, a review of the data will be conducted by a physician and a clinical review team at Abbott Laboratories.

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Confidential
ABBT0065867

ABT-594
Protocol M99-114
February 8, 2000

39

The SF-36™ Health Status Survey (Acute) will be recorded directly on the CRF and will be considered source data.

All CRFs must be legible and completed in black ball point ink. All corrections must be initialed and dated by the investigator or designated assistant. The investigator will review the CRFs for completeness and accuracy and sign and date the set of case report forms where indicated.

Each CRF will be printed on 3-part NCR paper. The forms consist of a white, yellow and pink copy. The white and yellow copy of the completed, verified CRF will be collected by the CRA and the pink copy retained at the investigative site.

Data captured on the CRF will be entered into the database by a double-key entry procedure at Abbott Laboratories. Discrepancies against the hard-copy CRF will be reviewed and corrected on-line. After completion of the entry process, computer logic checks will be run to check for such items as inconsistent study dates and outlying laboratory values, and any necessary corrections will be made to the database and documented via addenda or audit trail.

The laboratory results will be electronically transferred from the central laboratory to the study database. A final review of all laboratory results will be conducted by a physician and clinical review team at Abbott Laboratories.

9.7 Statistical Methods and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

All statistical tests will be 2-tailed and considered statistically significant if the P-value (Type 1 error rate) is less than or equal to 0.05 (when rounded to 3 decimal places).

For all efficacy and safety endpoints, comparisons of primary interest will be between each ABT-594 dose group and the placebo group, along with an assessment of ABT-594 linear dose response. Appropriate secondary comparisons will be made as considered necessary. No statistical adjustments will be made for multiple comparisons.

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ABBT0065868

ABT-594
Protocol M99-114
February 8, 2000

40

The baseline for all variables (except for the diary-based Pain Rating Scale) will be the last measurement obtained prior to receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale will be the average of the last 7 pain scores prior to receiving the first dose of blinded study drug on Day 1.

9.7.1.1 Data Sets Analyzed

Efficacy analyses will be performed for 2 sets of data: intent-to-treat subjects and evaluable subjects. Subjects receiving at least 1 dose of study drug with at least 1 diary-based baseline and at least 1 post-dose pain assessment for the diary-based Pain Rating Scale (11-Point Likert) will be included in the intent-to-treat analyses. The evaluable dataset will include subjects that receive at least 7 days of study drug with at least 1 baseline and at least 1 post Day 7 pain assessment for the diary-based Pain Rating Scale. Safety analyses will be performed with all randomized subjects who receive at least 1 dose of study drug.

9.7.1.2 Demographic and Other Baseline Characteristics

Baseline comparability among treatment groups for the reasons for premature discontinuation, demographic and baseline pain assessment measurements will be assessed. The analyses will be performed using 1 or more of the following methods: a 1-way analysis of variance (ANOVA) with treatment group as the main effect for quantitative variables, the Cochran-Mantel-Haenszel (CMH) test for equal row means for ordered categorical variables, and the Fisher's exact test (or its generalization to $r \times c$ tables) for qualitative variables.

9.7.1.3 Efficacy Analyses

For all efficacy variables (except the diary-based Pain Rating Scale), the baseline measurement will be the last measurement obtained prior to receiving the first dose of blinded study drug on Day 1. Baseline for the diary-based Pain Rating Scale will be the average of the last 7 pain scores prior to Day 1 of the study. Change from baseline to each scheduled evaluation will be calculated for all efficacy variables (except both Global Impression of Change scores).

ABT-594
Protocol M99-114
February 8, 2000

41

Primary Efficacy Analysis

The primary efficacy measurement will be the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert) score from each subject's diary to the corresponding average of the last 7 days on study drug.

Treatment groups differences for the primary efficacy variable will be evaluated using a 2-way ANOVA with factors for treatment group, study center, and the treatment group by study center interaction. If the interaction term is not statistically significant at the 0.10 level, the primary efficacy analysis for the treatment group differences will be the 2-way ANOVA with factors for treatment group and study center, but without the interaction term. If some study centers have fewer than 1 subject per treatment group in the intent-to-treat dataset, data from such centers will be combined for analysis.

Secondary Efficacy Analysis

Treatment group differences in the mean change from baseline to the final evaluation for the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), including 8 sub-domains and PCS and MCS, and the site-based Pain Rating Scale (11-Point Likert) score will be assessed using a 2-way ANOVA as described in the above Primary Efficacy Analysis subsection. The actual scores of each of the Subject and Clinician Global Impression of Change will be analyzed using the CMH test for equal row means with study centers as strata. SF-36™ PCS and MCS may also be analyzed using appropriate regression analysis (with possible factors for demographic variables, treatment and time).

Additionally, treatment group differences in the change from baseline to each scheduled evaluation will be assessed, as described for the change from baseline to the final evaluation for the Neuropathic Pain Scale and the site-based Pain Rating Scale (11-Point Likert). For the diary-based Pain Rating Scale (11-Point Likert), change from baseline to each scheduled evaluation will be analyzed using the last 7 days prior to each scheduled visit. Subject and Clinician Global Impression of Change will be evaluated using CMH methodology on actual scores.

ABT-594
Protocol M99-114
February 8, 2000

42

If indicated, exploratory analyses will be performed on change from baseline pain scores, such as analysis of covariance (ANCOVA), with baseline pain scores as the covariate.

Dose response for ABT-594 will be explored using both a parametric regression model and nonparametric tests, with and without placebo included. If the effect of investigator sites is not significant, then the nonparametric Jonckheere-Terpstra test will be used instead of Page's test to assess dose response of ABT-594.

Other analyses will be performed as appropriate.

Missing Data

Two sets of analyses, corresponding to the handling of missing observations, will be performed on the efficacy variables. The "last observation carried forward" (LOCF) analyses will use the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every subject in the analysis will have data for each specified evaluation. This technique reduces the bias caused by subjects who prematurely terminate for lack of efficacy. The "observed cases" (OC) analysis will not estimate the missing evaluation, and a subject who does not have pain evaluation on a scheduled visit will be excluded from the OC analysis for that visit.

In the event of data missing from the individual items in the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute), the estimated score of the missing item will be calculated, when less than one-half (within the scale of interest) of items are non-missing, as follows:

1. Calculate the ratio of the total score of the scale (the non-missing items) divided by the maximum possible total score for the non-missing items,
2. Multiply the maximum possible scores for the missing item by the ratio obtained in Step 1 above.

ABT-594
Protocol M99-114
February 8, 2000

43

9.7.1.4 Safety Analyses

All subjects receiving at least 1 dose of study drug will be evaluated for safety.

Adverse events will be coded using the COSTART V⁶ dictionary. Treatment-emergent adverse events (i.e., those which begin or worsen in severity after randomized study drug is taken) will be tabulated by body system and COSTART term for each treatment group. Treatment group differences will be evaluated using Fisher's exact test for the proportion of subjects reporting a particular adverse event. A summary of the severity, relationship to study drug, incidence and prevalence across time of all treatment-emergent adverse events, tabulated by COSTART term and body system, will be presented for each treatment group. Analyses by subgroup will be performed as appropriate.

Laboratory data will be analyzed using a 1-way ANOVA with treatment as the main effect. The primary analyses will be on the change from baseline to the minimum, maximum and final values during the study for each laboratory variable.

Additionally, the number and percentage of subjects with shifts from baseline to the final values using criteria for limits for statistical analysis and normal ranges to define categories (low, normal, high and missing) will be summarized.

Laboratory data values will be categorized as low, normal, or high based on normal ranges of the central laboratory used in this study. Low or high laboratory values will be flagged in the data listings. In addition, laboratory results which satisfy the criteria for limits for statistical analysis (Appendix I) will be identified.

Mean changes from baseline to the minimum, maximum and final values for vital signs and ECG will be analyzed in a similar manner as described for laboratory data above. Vital sign and ECG results which satisfy the criteria for below and above limits (Appendix I) will be identified.

Concurrent medication use will be summarized by treatment group.

Additional safety analyses will be performed as indicated.

ABT-594
Protocol M99-114
February 8, 2000

44

9.7.2 Determination of Sample Size

The study is designed to enroll approximately 320 subjects (approximately 80 subjects in each treatment group). This sample size will allow for the detection of a 0.46 effect size in the average diary-based Pain Rating Scale score for change from baseline to the final evaluation between any ABT-594 treatment group and placebo at 0.05 (two-tailed Type I error) level with at least 80% power. This calculation is based on results obtained from Study M98-833 of ABT-594 and published data using Gabapentin for subjects with painful diabetic polyneuropathy⁷ and assuming a 39% and 25% improvement from baseline for ABT-594 and placebo, respectively.

9.7.3 Pharmacokinetics/Pharmacodynamics

The maximum observed plasma concentration (C_{max}), the time to C_{max} (T_{max}), and the trough plasma concentration (C_{trough}) will be obtained directly from the plasma concentration-time data. The area under the plasma concentration-time curve during a dosing interval (AUC) will be obtained by the trapezoidal rule, using the Hour 0 concentration value for the Hour 12 value, or by some other appropriate methodology.

To assess dose proportionality and time invariance, T_{max} , dose-normalized C_{trough} and log-transformed dose-normalized AUC and C_{max} from the subset of subjects participating in the additional pharmacokinetic (PK) sampling will be subjected to a mixed effects model analysis. The model will include dose, visit (Visit I and Visit IV), and dose by visit interaction as fixed effects. Age, body weight, nicotine use status, and other variables that might account for variability in pharmacokinetics will be included as covariates. The study center factor will be included in the initial model, including a center main effect and, as appropriate, interaction of center with other factors. The center factor, or at least the interaction terms involving center, may be dropped from the model if they explain little of the variability in the data. If the number of subjects who have only Visit I data and not Visit IV data exceeds 20% of the subjects with intensive PK sampling, then analyses will also be performed for each visit separately. The hypothesis of invariance with dose will be tested by comparing the 300 µg BID dose vs the 150 µg BID dose. If the hypothesis of dose proportionality is rejected in a comparison, then the

ABT-594
Protocol M99-114
February 8, 2000

45

225 µg BID dose will be compared to each of the 150 and 300 µg BID doses. If the visit by dose interaction is statistically significant, then a comparison will be made for each visit.

An exploratory analysis will also be performed on the data set obtained from all subjects (including those who do not participate in the intensive PK sampling). This analysis will appropriately take into account the time of sampling relative to dosing. The questions of dose proportionality and change from Visit I to Visit IV will be considered in this analysis.

If there is some evidence from the data of this study that ABT-594 is efficacious, then the relationship between ABT-594 plasma concentration and the primary efficacy variable will be explored, using data from ABT-594 and placebo treatment groups or from ABT-594 treatment groups alone. One exploration will utilize the data of all subjects. An analysis using only the data of subjects undergoing intensive PK sampling may also be done. The model will include effects for efficacy variable baseline value and for visit. The center factor will be incorporated appropriately. The dependency of the measurements from the same subject will be accounted for.

Other analyses may be performed as necessary.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Changes

This study will be conducted in accordance with the protocol, GCP, all applicable local, state federal regulations and regulatory requirements. Neither the investigator nor the CRO will modify this protocol without first obtaining the concurrence of Abbott Laboratories. The modification must be documented in writing. Any change in the research activity, except those necessary to remove an apparent immediate hazard to the subject or those of an administrative or clarifying nature, must be reviewed and approved by the Institutional Review Board before implementation. Abbott Laboratories must submit protocol amendments to the FDA and possibly to other government agencies.

This study will be terminated if these conditions are not met.

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ABBT0065874

ABT-594
Protocol M99-114
February 8, 2000

46

10.0 Protocol Deviations

When deviation from the protocol is deemed necessary for an individual subject, the investigator or other physician in attendance must contact the site study monitor at the CRO, who will contact Abbott Laboratories. Such contact will be made as soon as possible to permit a decision as to whether or not the subject is to continue in the study. Any departures from the protocol will be authorized only for that one subject. A description of the departure from the protocol and the reason for it will be recorded on the CRF.

11.0 Use of Information and Publication

All information concerning ABT-594 and Abbott Laboratories' operations, such as Abbott Laboratories' patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Abbott Laboratories and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Abbott Laboratories in connection with the development of ABT-594. This information may be disclosed as deemed necessary by Abbott Laboratories. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide Abbott Laboratories with complete test results and all data developed in this study.

This confidential information shall remain the sole property of Abbott Laboratories, shall not be disclosed to others without the written consent of Abbott Laboratories, and shall not be used except in the performance of this study.

Should the investigator choose to publish the results of this study, a copy of the manuscript will be provided to Abbott Laboratories at least 90 days before the date of submission to the intended publisher.

Neither the subject nor their physician will be informed of individual subject pharmacogenetic results, should they be performed, nor will anyone not directly involved in this research. This is due to the fact that, 1) the subject and their physician are already

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ABBT0065875

ABT-594
Protocol M99-114
February 8, 2000

47

aware of the subject's particular response to the drug and the study information would not affect their future medical care, and 2) if an association is established between a genetic sequence and a treatment response, separate studies must be conducted in order to validate or confirm the results and the properties of the test prior to the necessary regulatory approval to use the test for diagnostic purposes. DNA samples from this protocol may be used either for gene identification, validation, or diagnostic test development studies, as well as discovery of genes related to painful diabetic polyneuropathy.

12.0 Completion of The Study

The investigator will complete and report this study in satisfactory compliance with the protocol within 9 months after receipt of study supplies. Continuation of the study beyond this time must be mutually agreed upon in writing by both the investigator and Abbott Laboratories. It is agreed that, for reasonable cause, either the investigator or Abbott Laboratories (the sponsor), may terminate this study prematurely provided that written notice is submitted at a reasonable time in advance of the intended termination.

The investigator will retain all essential documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are not pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

ABT-594
Protocol M99-114
February 8, 2000

48

13.0 Investigator's Agreement

1. I have received and reviewed the Investigator Brochure for ABT-594.
2. I have read the protocol and agree to conduct the study as outlined and in accordance with all local, state, and federal regulations.
3. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)

IN/R-S/1/ABT594/99114/99114PRO/P25-49
GO2Q143011

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ABBT0065877

ABT-594
Protocol M99-114
February 8, 2000

49

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ABBT0065878

ABT-594
Protocol M99-114
February 8, 2000

50

Appendix A

Documents Required Prior to Initiation of the Study

As sponsor of a clinical study, Abbott Laboratories has an obligation to ensure that the study will be conducted by a qualified investigator with sufficient resources (of time, personnel, and physical facilities) to conduct the study and to ensure that the investigator understands and agrees to comply with applicable regulations, policies, and procedures. Prior to the beginning of any clinical study, the investigator will be asked to provide the following documentation.

1. A signed protocol for the study.
2. A signed Form FDA 1572 or equivalent document certifying the investigator's agreement to comply with U.S. Federal (21 CFR, ICH GCP Guidelines) regulations governing the conduct of the study.
3. A signed Abbott Financial Disclosure form.
4. A current curriculum vitae of the investigator. If sub-investigators will participate in the study, a curriculum vitae for each.
5. Requirements for the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
 - A copy of the letter of approval of the IRB/IEC. The letter must specify that both the protocol and consent form were approved.
 - The names and affiliations of the members of the IRB/IEC or assurance number.
 - If the principal and/or sub-investigator is a member of the IRB/IEC, a letter stating that he/she did not participate in the review or approval of the protocol or consent form.
6. A specimen copy of the IRB/IEC-approved informed consent document to be used in the study.
7. A list of normal ranges of values for all laboratory tests specified by the protocol for all laboratories utilized.
8. A copy of the laboratory(ies) certification(s) or the authorization number of the certification(s), the name of the certifying authority, and the period of certification.

As a rule, these documents will be provided in the course of one or more visits to the investigator by an Abbott Laboratories representative. Usually the study cannot begin until all of the documents listed above have been provided.

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ABBT0065879

ABT-594
Protocol M99-114
February 8, 2000

51

Appendix B

Declaration of Helsinki

Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, in June 1964.
Amended by the 29th World Medical Assembly, Tokyo, Japan, in October 1975,
35th World Medical Assembly, Venice, Italy, in October 1983,
41st World Medical Assembly, Hong Kong, in September 1989 and
48th General Assembly, Somerset West, Republic of South Africa 1996.

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words "The health of my patient will be my first consideration" and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

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Confidential
ABBT0065880

ABT-594
Protocol M99-114
February 8, 2000

52

Appendix B (Cont.)

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

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Confidential
ABBT0065881

ABT-594
Protocol M99-114
February 8, 2000

53

Appendix B (Cont.)

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obligated to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in the Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.
10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

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ABBT0065882

ABT-594
Protocol M99-114
February 8, 2000

54

Appendix B (Cont.)

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic methods. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician - patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I.2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Patients (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

REASON FOR REVISION: Revised to correspond to the amendment adopted by the 48th General Assembly of the World Medical Association, Somerset West, Republic of South Africa 1996.

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ABT-594
Protocol M99-114
February 8, 2000

55

Appendix C

Responsibilities of the Clinical Investigator

Clinical research studies sponsored by Abbott Laboratories are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is actually a form letter addressed to the sponsor (Abbott Laboratories), summarizing the investigators qualifications for the study and their willingness to follow FDA regulations with respect to the study.

In signing a Form FDA 1572, the investigator agrees to assume the following responsibilities:

1. To secure prior approval of the study by an appropriate institutional review board which conforms to FDA regulations.
2. To make at least yearly reports on the progress of the study to the above committee, and a final report within three months of study completion.
3. To maintain current running records of the receipt, administration, and disposition of study medication and to return all unused study medication to Abbott Laboratories.
4. To obtain valid written informed consent from each patient who participates in the study.
5. To prepare and maintain adequate case histories of all persons entered into the study, including case report forms, hospital records, laboratory results, etc., and to maintain these data for a minimum of two years following notification by Abbott Laboratories that all investigations have been discontinued with this drug.
6. To identify all subinvestigators who will also supervise drug administration.
7. To report adverse effects to Abbott Laboratories promptly. In the event of serious or unexpected adverse event, to notify Abbott Laboratories immediately by telephone.
8. To allow possible inspection and copying by the FDA of case reports and records of drug distribution.

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ABT-594
Protocol M99-114
February 8, 2000

56

Appendix D

Elements of the Consent Form

Abbott Laboratories requires that all informed consent statements used in studies which they sponsor comply with FDA 21 CFR 50 (Protection of Human Subjects) and the ICH Good Clinical Practice Guideline. To ensure compliance, the informed consent itemization listed below is provided to guide the investigator in drafting an acceptable informed consent. Abbott Laboratories will review a proposed informed consent prior to its submission to the Review Committee (Institutional Review Board, Ethics Committee); alternatively, Abbott will supply to the investigator a draft informed consent statement which may be submitted to the review Committee.

For IND Studies, procedures will comply with FDA 21 CFR 50 and the ICH Good Clinical Practice Guideline.

Signed informed consent will be obtained from all patients participating in PPD Clinical Research studies or the patients' legally authorized representative. This consent must include the following items:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The approximate number of patients involved in the trial.
4. The expected duration of the patient's participation.
5. The trial treatment(s) and the probability for random assignment to each treatment.
6. Identification of experimental procedures.
7. The trial procedures to be followed, including all invasive procedures.
8. The patient's responsibilities.
9. A description of any reasonably foreseeable risks or inconveniences to the patient and, if applicable, to an embryo, fetus, or nursing infant.
10. A statement that may involve risks which are currently unforeseeable.
11. The anticipated expenses, if any, to the patient for participating in the trial.
12. A description of the reasonable expected benefits. If there is no intended clinical benefit to the patient, this should be stated.

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ABBT0065885

ABT-594
Protocol M99-114
February 8, 2000

57

Appendix D (Cont.)

13. The anticipated prorated payment, if any, to the patient for participating in the trial.
14. The alternative procedure(s) or course(s) of treatment that may be available to the patient, and their important potential benefits and risks.
15. A statement that the patient or the patient's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the patient's willingness to continue participation in the trial.
16. An explanation as to whether any compensation or medical treatment are available if injury occurs. If so, what the compensation consists of and/or where further information may be obtained.
17. Whom to contact about information regarding the trial.
18. Whom to contact about research patient's rights (ideally not the investigator).
19. Whom to contact in the event of trial-related injury of the patient.
20. A statement that the monitor(s), auditor(s), the IRB/EC, and regulatory authorities (e.g., FDA) will be granted direct access to the patients' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the patient, to the extent permitted by the applicable laws and regulations and that, by signing a written consent form, the patient or the patient's legally acceptable representative is authorizing such access.
21. A statement that the site will collect information on the patient per ICH requirements, including patient name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who can be contacted in an emergency will also be recorded. This information will be treated with strict adherence to professional standards of confidentiality and will be filed at the site.
22. A statement that the records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the patient's identity will remain confidential.
23. The foreseeable circumstances and/or reasons under which the patients' participation in the trial may be terminated.

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ABT-594
Protocol M99-114
February 8, 2000

58

Appendix D (Cont.)

24. Procedures for orderly termination of participation.
25. A statement that participation is voluntary.
26. A statement that refusal to participate will involve no penalty or loss of benefits.
27. A statement that the patient may discontinue participation at any time without penalty or loss of benefits.
28. A statement that a signed and dated copy of the consent is given to the patient.
29. The statement, "I agree to participate..."
30. A place for the patient or the patient's legally acceptable representative to sign and date.
31. A place for the person who conducted the informed consent discussion to sign and date.

Appendix E
Sample Abbott Laboratories Drug Accountability Form
Study M99-114

ABT-594
 Protocol M99-114
 February 8, 2000

Subject Randomization Number: ♦ _____ Subject Initials: _____ Subject Birthdate: _____

Investigator's Name: _____ Location: _____

	Module Carton Type	Module # ♦	NPRO #	Clinical Supplies Invoice No.	Date Received (M/D/Y)
Baseline Visit	Days 1-7				
Baseline Visit	Days 8-49				
Visit II	Days 8-49				
Visit III	Days 8-49				

Visit	DISPENSED TO SUBJECT					RETURNED FROM SUBJECT			VERIFIED BY CRA	
	Module # ♦	# Capsules	Date	By*	Checked By	Date	No. of Capsules Remaining	By*	By*	Date
Baseline Visit	Days 1-7	52								
	— — — — —									
	Days 8-49	144								
	— — — — —									
Visit I	Redispense balance of Days 8-49 cards remaining from Baseline Visit	— — — — —								
Visit II	— — — — —	144								
Visit III	— — — — —	144								

* Pharmacist/Coordinator/Nurse

+ CRO Monitor

♦ Assigned by IVRS

59

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ABT-594
Protocol M99-114
February 8, 2000

60

Appendix F

Pain Assessments

Pain Rating Scale (11 point Likert)

The subject's pain intensity will be assessed by completion of the following statement in the daily diaries and at the investigative site.

How severe was your neuropathy pain during the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Pain Possible

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ABT-594
Protocol M99-114
February 8, 2000

61

Appendix G

Neuropathic Pain Scale

Instructions: There are several different aspects of pain which we are interested in measuring: pain sharpness, heat/cold, dullness, intensity, overall unpleasantness, and surface vs. deep pain.

The distinction between these aspects of pain might be clearer if you think of taste. For example, people might agree on how *sweet* a piece of pie might be (the *intensity* of the sweetness), but some might enjoy it more if it were sweeter while others might prefer it to be less sweet. Similarly, people can judge the loudness of music and agree on what is more quiet and what is louder, but disagree on how it makes them feel. Some prefer quiet music and some prefer it more loud. In short, the *intensity* of a sensation is not the same as how it makes you feel. A sound might be unpleasant and still be quiet (think of someone grating their fingernails along a chalkboard). A sound can be quiet and "dull" or loud and "dull."

Pain is the same. Many people are able to tell the difference between many aspects of their pain: for example, *how much* it hurts and *how unpleasant* or annoying it is. Although often the intensity of pain has a strong influence on how unpleasant the experience of pain is, some people are able to experience more pain than others before they feel very bad about it.

There are scales for measuring different aspects of pain. For one patient, a pain might feel extremely hot, but not at all dull, while another patient may not experience any heat, but feel like their pain is very dull. We expect you to rate very high on some of the scales below and very low on others. We want you to use the measures that follow to tell us exactly what you experience.

1. Please use the scale below to tell us how intense your pain is. Place an "X" through the number that best describes the intensity of your pain.												
No pain	<table border="1" style="display: inline-table; text-align: center; width: 100%;"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10
0	1	2	3	4	5	6	7	8	9	10		
	The most intense pain sensation imaginable											
2. Please use the scale below to tell us how sharp your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts."												
Not sharp	<table border="1" style="display: inline-table; text-align: center; width: 100%;"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10
0	1	2	3	4	5	6	7	8	9	10		
	The most sharp sensation imaginable ("like a knife")											
3. Please use the scale below to tell us how hot your pain feels. Words used to describe very hot pain include "burning" and "on fire."												
Not hot	<table border="1" style="display: inline-table; text-align: center; width: 100%;"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10
0	1	2	3	4	5	6	7	8	9	10		
	The most hot sensation imaginable ("on fire")											
4. Please use the scale below to tell us how dull your pain feels. Words used to describe very dull pain include "like a dull toothache," "dull pain," "aching" and "like a bruise."												
Not dull	<table border="1" style="display: inline-table; text-align: center; width: 100%;"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> </table>	0	1	2	3	4	5	6	7	8	9	10
0	1	2	3	4	5	6	7	8	9	10		
	The most dull sensation imaginable											

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ABT-594
Protocol M99-114
February 8, 2000

62

Appendix G (Cont.)

5.	Please use the scale below to tell us how cold your pain feels. Words used to describe very cold pain include "like ice," and "freezing."											
Not cold	0	1	2	3	4	5	6	7	8	9	10	The most cold sensation imaginable ("freezing")
6.	Please use the scale below to tell us how sensitive your skin is to light touch or clothing. Words used to describe sensitive skin include "like sunburned skin" and "raw skin."											
Not sensitive	0	1	2	3	4	5	6	7	8	9	10	The most sensitive sensation imaginable ("raw skin")
7.	Please use the scale below to tell us how itchy your pain feels. Words used to describe itchy pain include "like poison oak" and "like a mosquito bite."											
Not itchy	0	1	2	3	4	5	6	7	8	9	10	The most itchy sensation imaginable ("like poison oak")
8.	Now that you have told us the different physical aspects of your pain, the different types of sensations, we want you to tell us overall how unpleasant your pain is to you. Words used to describe very unpleasant pain include "miserable" and "intolerable." Remember, pain can have a low intensity, but still feel extremely unpleasant, and some kinds of pain can have a high intensity but be very tolerable. With this scale, please tell us how unpleasant your pain feels.											
Not unpleasant	0	1	2	3	4	5	6	7	8	9	10	The most unpleasant sensation imaginable ("intolerable")
9.	Lastly, we want you to give us an estimate of the severity of your <u>deep</u> versus <u>surface</u> pain. We want you to rate each location of pain separately. We realize that it can be difficult to make these estimates, and most likely it will be a "best guess," but please give us your best estimate.											
HOW INTENSE IS YOUR DEEP PAIN?												
No deep pain	0	1	2	3	4	5	6	7	8	9	10	The most intense deep pain sensation imaginable
HOW INTENSE IS YOUR SURFACE PAIN?												
No surface pain	0	1	2	3	4	5	6	7	8	9	10	The most intense surface pain sensation imaginable

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ABT-594
Protocol M99-114
February 8, 2000

63

Appendix H
Subject Global Impression of Change and
Clinician Global Impression of Change

Subject Global Impression of Change

The subject's impression of pain relief will be assessed by completion of the following statement:

Compared to the Baseline Pain Assessment Phase, how much have you changed overall?

- 1 Much Improved
- 2 Moderately Improved
- 3 Minimally Improved
- 4 No Change
- 5 Minimally Worse
- 6 Moderately Worse
- 7 Much Worse

Clinician Global Impression of Change

The clinicians impression of pain relief will be assessed by completion of the following statement:

Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to Baseline, how much has the subject changed overall?

- 1 Much Improved
- 2 Moderately Improved
- 3 Minimally Improved
- 4 No Change
- 5 Minimally Worse
- 6 Moderately Worse
- 7 Much Worse

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ABT-594
Protocol M99-114
February 8, 2000

64

Appendix I
Laboratory Determinations, Vital Signs and Electrocardiogram
Variables for Statistical Analysis

Hematology	Below Limit	Above Limit
Hemoglobin (g/dL)		
Female	≤ 9.5	≥ 16.5
Male	≤ 11.5	≥ 18.5
Hematocrit (%)		
Female	≤ 32	≥ 50
Male	≤ 37	≥ 55
Red Blood Cells ($\times 10^{12}/L$)		
Female	≤ 3.5	≥ 6.0
Male	≤ 3.8	≥ 7.0
White Blood Cells ($\times 10^9/L$)	≤ 2.8	≥ 16.0
Platelet Count ($\times 10^9/L$)	≤ 75	≥ 700
Eosinophils (%)		≥ 10
Basophils (%)		≥ 10
Lymphocytes (%)		≥ 75
Monocytes (%)		≥ 15
Neutrophils (%)	≤ 15	
Bands (%)		≥ 10
Mean Corpuscular Volume (fL)	$\leq 0.8 \times \text{LLN}$	$\geq 1.2 \times \text{ULN}$
Mean Corpuscular Hemoglobin Concentration (g/dL)	$\leq 0.8 \times \text{LLN}$	$\geq 1.2 \times \text{ULN}$
Atypical Lymphocytes (%)		≥ 5
Prothrombin Time (sec)		$\geq 2 \text{ ULN}$
Partial Thromboplastin Time (sec)		$\geq 2 \text{ ULN}$

LLN = Lower limit of normal ULN = Upper limit of normal

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ABT-594
Protocol M99-114
February 8, 2000

65

Appendix I (Cont.)

Chemistry	Below Limit	Above Limit
Albumin (g/dL)	≤ 2.5	
Alkaline Phosphatase (IU/L)		$\geq 3 \times \text{ULN}$
Bicarbonate (mEq/L)	≤ 12	≥ 38
BUN (mg/dL)		≥ 30
Calcium (mg/dL)	≤ 8.2	≥ 12
Chloride (mEq/L)	≤ 90	≥ 118
Cholesterol (mg/dL)		≥ 600
Creatinine (mg/dL)		≥ 2.0
Direct Bilirubin (mg/dL)		≥ 2.0
Glucose (mg/dL)	≤ 45	≥ 175
LDH (IU/L)		$\geq 3 \times \text{ULN}$
Inorganic Phosphorus (mg/dL)	≤ 1.7	≥ 5.5
Potassium (mEq/L)	≤ 3.0	≥ 6.0
SGOT/AST (IU/L)		$\geq 3 \times \text{ULN}$
SGPT/ALT (IU/L)		$\geq 3 \times \text{ULN}$
Sodium (mEq/L)	≤ 126	≥ 156
Total Bilirubin (mg/dL)		≥ 2.0
Total Protein (g/dL)	≤ 4.5	≥ 10
Triglycerides (mg/dL)		≥ 600
Uric acid (mg/dL)		
Female		≥ 8.5
Male		≥ 10.5

ULN = Upper limit of normal

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ABT-594
Protocol M99-114
February 8, 2000

66

Appendix I (Cont.)

Urinalysis	Below Limit	Above Limit
Specific Gravity	≤ 1.001	≥ 1.030
PH	≤ 4	≥ 9
Protein		$\geq 3+^*$ (≥ 10)
Ketones		$\geq 3+^*$
RBC		
Female		$\geq 10/\text{hpf}$
Male		$\geq 8/\text{hpf}$
WBC		$\geq 10/\text{hpf}$ ($\geq 2+$)
Casts		≥ 9
Glucose		$\geq 3+^*$
Oral Body Temperature		
Temperature	Low: decreased $\geq 2^\circ\text{F}$ from baseline High: $\geq 101^\circ\text{F}$	
Body Weight		
Weight	Low: decreased $\geq 15\%$ from baseline High: increased $\geq 15\%$ from baseline	
Supine or Sitting Vital Signs		
Systolic Blood Pressure	Low: ≤ 90 mmHg and decreased ≥ 30 from baseline High: ≥ 180 mmHg and increased ≥ 40 from baseline	
Diastolic Blood Pressure	Low: ≤ 50 mmHg and decreased ≥ 20 from baseline High: ≥ 105 mmHg and increased ≥ 30 from baseline	
Heart Rate	Low: ≤ 50 bpm and decreased ≥ 30 bpm from baseline High: ≥ 120 bpm and increased ≥ 30 bpm from baseline	

* $\geq 3+$ on a scale with 4+ being the maximum value

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ABT-594
Protocol M99-114
February 8, 2000

67

Appendix I (Cont.)

Electrocardiogram	
PR Interval	High: ≥ 210 msec
QRS Duration	Low: ≤ 50 msec
	High: ≥ 150 msec
QT Interval	Low: ≤ 200 msec
	High: ≥ 500 msec
QTc Interval*	Low: ≤ 200 msec
	High: ≥ 500 msec
Heart Rate	Low: ≤ 50 bpm and decreased ≥ 30 bpm from baseline
	High: ≥ 120 bpm and increased ≥ 30 bpm from baseline

* QTc calculated as QT divided by the square root of RR interval

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EX. 18



Christopher J
Silber/LAKE/PPRD/ABBOTT
05/16/2000 04:12 PM

To Grace C Dunn/LAKE/PPRD/ABBOTT@ABBOTT, Ann P
Sullivan/LAKE/PPRD/ABBOTT@ABBOTT
John M Leonard/LAKE/PPRD/ABBOTT@ABBOTT, Steve
Cohen/LAKE/PPRD/ABBOTT@ABBOTT, Barbara T
cc Massa/LAKE/PPRD/ABBOTT@ABBOTT, Susan A
Hanson/LAKE/PPRD/ABBOTT@ABBOTT, Thomas E
Woidat/LAKE/PPRD/ABBOTT@ABBOTT

bcc

Subject Monthly highlights

Ann/Grace:

Below are the monthly highlights for the Analgesia Venture

"The Go/No Go milestone was achieved on schedule. ABT-594 data presented at the October 6, 1999 Portfolio Review included Phase 2 results on the M98-833 Neuropathic Pain and M98-826 Osteoarthritis Pain studies (maximum dose 75 mcg BID). Based on the data it was decided that the ABT-594 program will continue with the identification of maximum tolerated doses (MTD), with and without titration, of the hard gelatin capsule (HGC) dosage form, and assessment of these higher doses in Phase2.

Study M99-076 has been completed, and the MTD of ABT-594 (without titration) is 300 mcg BID. Study M99-120 has also been completed, and has provided evidence that titration improves the tolerability of ABT-594.

Study M99--114 (Diabetic Neuropathy pain), a 7 week placebo controlled study of titrated doses of ABT-594 150 mcg, 225 mcg and 300 mcg BID has been initiated (first patient randomized on 4/24), with 24/30 sites supplied with study drug. Study M99-115 (Osteoarthritis pain) is on hold (blue-plan)."

Please call if you have questions.

Chris

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ABBT364740

EX. 20



Marilyn J.
Collicott / LAKE / PPRD / ABBO
TT
12/14/2000 12:20 PM

To JSCHANZENBACH@rsi-nc.com@internet
cc
bcc
Subject Study Termination

Hi John

We've decided to end enrollment as of 1/5/01. The attached letter (which explains our reasoning) will be fedexed out to all investigators today. You may get some phone calls tomorrow. Let me know if you have any questions. Thanks.....mc

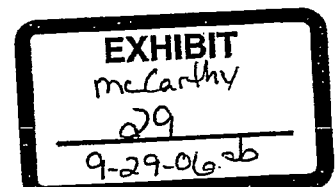


stopenroll

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Silber
DEP. EX. NO. 39
FOR ID., AS OF 2-9-07 BC

ABBT233539



December 14, 2000

<name>
<address>

RE: Protocol M99-114: A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Neuropathy

Dear Dr. <name>,

We have decided to end enrollment in the above referenced study on January 5, 2001.

As specified in the protocol, 80% power would have been achieved with the randomization of 320 subjects, assuming there were no premature terminations. Our current premature termination rate, however, will result in less than 80% power even if we were to reach our enrollment goal. After reviewing possible outcomes with our statisticians, we concluded that ending enrollment prior to reaching our goal of 320 subjects will not meaningfully change our ability to interpret the results of this study. In addition, the sooner we review the data from M99-114, the sooner we may be able to move forward into Phase III.

In order to allow you to enroll any subjects that may have already been scheduled, the last date for randomization into study M99-114 will be 1/5/01. We sincerely apologize if this causes you or your staff any inconvenience.

The Analgesia Venture thanks you for your hard work and dedication to ABT-594 and study M99-114. Your efforts have allowed us to move forward more quickly than anticipated. If you have any questions or concerns please don't hesitate to contact me.

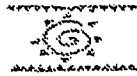
Sincerely,

Marilyn Collicott
Clinical Project Manager
Analgesia Venture

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ABBT233540

EX. 24



Bruce McCarthy
10/23/2001 09:24 AM

To: Philip M Deemer/LAKE/CORP/ABBOTT@ABBOTT
cc: James Sullivan/LAKE/PPRD/ABBOTT@ABBOTT
Subject: Re: Non-confidential briefing on ABT-594

will send my comments by fax (had printed out your file and edited)--let me know if you're unable to read the comments.

Your document (with the competition section) got me thinking to add a few more potential companies:

Purdue
J&J
Targacept
Icagen
Elan
Mallinkrodt
TAP
Takeda
Endo
Adolor
Pain Therapeutics
Sepracor
Pfizer
Lundbeck
Sanofi-Synthelabo
AstraZeneca
GSK
Boehringer Ingelheim
Novartis
Aventis
Esteve
Cambridge Neuroscience
Taisho

Philip M Deemer

Philip M Deemer
10/22/2001 04:30 PM

To: James Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Bruce
McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Michael K
Blamesen/LAKE/PPRD/ABBOTT@ABBOTT, Danhui
Wang/LAKE/PPD/ABBOTT@ABBOTT
cc:
Subject: Non-confidential briefing on ABT-594

The attached is what we used for Hancock as the conf disclosure. Pls. suggest revisions so that we can use this as a non-confidential disclosure.

Thank you.



ABT-594 201.doc

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ABBT0165038

EX. 28



From the Office of the Executive V.P. Pharmaceuticals & Chief Scientific Officer

Jeffrey M. Leiden, M.D., Ph.D.

To: M. Beatrice
C. Begley
B. Dempsey
D. Goffredo
R. Gonzalez
M. Heath-Chiozzi
B. Kamen
J. Leonard
D. Norbeck
E. Ogunro
J. Tyree
S. Weger
L. Wyatt

cc: J. Arnott
B. Ford
S. Bukotzer
S. Nibhuachalla
E. Sun
J. Wenker

Re: Summary of 12/10/01 PEC Meeting

The December 10 PEMC meeting focus was on the anti-infective franchise with specific discussions on ABT-773 and ABT-492. Jerry Wenker's and John Arnott's teams prepared a thorough analysis of the current development status of each of the noted products. The following decisions were made by the PEC:

ABT-773

- The project should be put on hold. Do not start any new studies or activities. Existing studies and projects should be continued.
- Jim Tyree will aggressively pursue out-licensing or selling the compound.

ghly Confidential

ABBT209487

Leonard
FOR I.D. 6/1/07 **EXHIBIT** 45
1.00

- The team is to prepare a 30 minute presentation for Miles White which summarizes the issues and presents the recommendations. The meeting should take place in December 2001.

-

ABT-492

- The team is to generate a product profile for the compound which defines the performance parameters for commercial success.
- A Phase II program should be designed to stress the defined profile parameters.
- Do not start additional, Phase II studies until approved by PEC

Other

- Funding was not authorized for the ketolide backup compounds discussed.
- Jim Tyree will aggressively pursue licensing/acquisition rights to Gatifloxacin

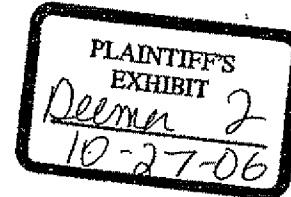
Future PEMC Agenda Items

- January Meeting
 - Review Omnicef R/D spending against the product profitability and present alternatives.

February Meeting

- Review the Clari life-cycle management opportunities.
- Review the Pump Inhibitor Program status.

EX. 32



RESEARCH FUNDING AGREEMENT

by and between

ABBOTT LABORATORIES

and

JOHN HANCOCK LIFE INSURANCE COMPANY,

JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY,

and

INVESTORS PARTNER LIFE INSURANCE COMPANY

dated as of

March 13, 2001.

Plt/Def: _____
Exhibit No.: 4
Witness: TUCKER
Date: 6-27-07
Maria A. Hasakian, CSR No. 8469

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INDEX

INDEX OF DOCUMENTS

<u>Tab No.</u>	<u>Document</u>
1.	Research Funding Agreement dated as of March 13, 2001
2.	Exhibits to Research Funding Agreement
3.	Legal opinion of Brian J. Smith
4.	Proposed Summary of Terms dated June 27, 2000
5.	Miscellaneous Choate, Hall & Stewart memoranda
6.	Miscellaneous Choate, Hall & Stewart memoranda to John Hancock regarding "outstanding issues"
7.	Miscellaneous correspondence between Choate, Hall & Stewart and Abbott Laboratories
8.	Copies of Choate, Hall & Stewart legal bills
9.	Working Group List

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RESEARCH FUNDING AGREEMENT

by and between

ABBOTT LABORATORIES

and

JOHN HANCOCK LIFE INSURANCE COMPANY,

JOHN HANCOCK VARIABLE LIFE INSURANCE COMPANY,

and

INVESTORS PARTNER LIFE INSURANCE COMPANY

dated as of

March 13, 2001

CONFIDENTIAL
JH 008078

-i-

TABLE OF CONTENTS

ARTICLE 1 - DEFINITIONS.....	1
ARTICLE 2 - ANNUAL RESEARCH PROGRAM.....	9
2.1 <u>Program Term</u>	9
2.2 <u>Research Plan</u>	9
2.3 <u>Conduct of Research</u>	10
2.4 <u>Subcontracting Research</u>	10
2.5 <u>Research Reports and Records</u>	10
ARTICLE 3 - RESEARCH FUNDING.....	11
3.1 <u>John Hancock Program Payments</u>	11
3.2 <u>Abbott Funding Obligation</u>	11
3.3 <u>Carryover Provisions</u>	11
3.4 <u>Termination of John Hancock's Program Payment Obligation</u>	12
3.5 <u>Hancock Funding Obligation</u>	13
ARTICLE 4 - PRODUCT RESEARCH AND DEVELOPMENT.....	13
4.1 <u>Commercially Reasonable Efforts</u>	13
4.2 <u>Marketing and Sale Responsibility</u>	13
4.3 <u>Failure of Program Compound to Progress</u>	14
4.4 <u>Arm's-Length</u>	16
4.5 <u>In-License Agreements</u>	16
ARTICLE 5 - PROGRAM INVENTIONS.....	17
5.1 <u>Ownership</u>	17
5.2 <u>Patent Prosecution and Maintenance</u>	17
5.3 <u>Enforcement</u>	17
ARTICLE 6 - MILESTONE PAYMENTS TO JOHN HANCOCK.....	17
6.1 <u>[Intentionally omitted]</u>	17
6.2 <u>Management Fee</u>	17
6.3 <u>Milestone Notification and Payments</u>	18
ARTICLE 7 - ROYALTIES.....	19
7.1 <u>Royalty Rates</u>	19
7.2 <u>Royalty Term</u>	19
ARTICLE 8 - ROYALTY REPORTS AND ACCOUNTING.....	20
8.1 <u>Reports, Exchange Rates</u>	20
8.2 <u>Audits</u>	20
8.3 <u>Confidential Financial Information</u>	21
8.4 <u>Accounting Principles</u>	21
ARTICLE 9 - PAYMENTS.....	22
9.1 <u>Payment Terms</u>	22
9.2 <u>Payment Method</u>	22
9.3 <u>Late Payments</u>	22
ARTICLE 10 - CONFIDENTIALITY.....	22

CONFIDENTIAL

JH 008079

-ii-

10.1	<u>Nondisclosure Obligations</u>	22
10.2	<u>Permitted Disclosures</u>	22
10.3	<u>Publicity Review</u>	23
ARTICLE 11- TERM AND TERMINATION		23
11.1	<u>Expiration</u>	23
11.2	<u>Termination; Material Breach</u>	23
11.3	<u>Effect of Expiration of Termination</u>	24
ARTICLE 12 - WARRANTIES AND INDEMNITY		24
12.1	<u>John Hancock Representations and Warranties</u>	24
12.2	<u>Abbott Representations and Warranties</u>	25
12.3	<u>No Conflict</u>	29
12.4	<u>Compliance with Law</u>	29
12.5	<u>No Other Warranties</u>	29
12.6	<u>Indemnification of John Hancock</u>	29
12.7	<u>Indemnification of John Hancock Relating to In-Licensed Compounds</u>	30
12.8	<u>Procedure</u>	30
12.9	<u>Insurance</u>	31
12.10	<u>Acknowledgment</u>	31
ARTICLE 13 - FORCE MAJEURE		31
ARTICLE 14 - ASSIGNMENT		31
ARTICLE 15 - SEVERABILITY		32
ARTICLE 16 - MISCELLANEOUS		32
16.1	<u>Notices</u>	32
16.2	<u>Applicable Law</u>	34
16.3	<u>Entire Agreement</u>	34
16.4	<u>Headings</u>	34
16.5	<u>Independent Contractors</u>	34
16.6	<u>Performance By Affiliates</u>	35
16.7	<u>Dispute Resolution</u>	35
16.8	<u>Waiver</u>	35
16.9	<u>Counterparts</u>	35

EXHIBIT 1.6:	First Annual Research Plan
EXHIBIT 1.17:	Eisai Territory
EXHIBIT 1.40:	Program Compounds
EXHIBIT 1.43:	Example of Program Related Costs for One Program Compound
EXHIBIT 9.2:	Payment Instructions
EXHIBIT 12.2(d):	Further Information regarding Program Compounds
EXHIBIT 12.2(e):	Certain Patent Information
EXHIBIT 12.2(f):	Communications
EXHIBIT 12.2(i):	Compound Reports

CONFIDENTIAL
JH 008080

RESEARCH FUNDING AGREEMENT

This Research Funding Agreement is made as of March 13, 2001, by and between Abbott Laboratories; an Illinois corporation ("Abbott"), with its principal offices at 100 Abbott Park Road, Abbott Park, Illinois 60064-6049, and John Hancock Life Insurance Company, a Massachusetts corporation, John Hancock Variable Life Insurance Company, a Massachusetts corporation, and Investors Partner Life Insurance Company, a Delaware corporation (collectively, "John Hancock"), each with its principal offices at 200 Clarendon Street, Boston, Massachusetts 02117.

WITNESSETH

WHEREAS, Abbott is a global healthcare company actively engaged in the research and development of human pharmaceutical products;

WHEREAS, Abbott is interested in obtaining additional funding to support such research and development activities with respect to certain pharmaceutical products which are under development; and

WHEREAS, John Hancock is interested in providing such additional funding in exchange for the right to receive future milestone and royalty payments from Abbott.

NOW, THEREFORE, in consideration of the foregoing and the mutual covenants and undertakings contained herein, the parties hereto agree as follows:

ARTICLE I
DEFINITIONS

In addition to the other terms defined elsewhere herein, the following terms shall have the following meanings when used in this Agreement (and any term defined in the singular shall have the same meaning when used in the plural and vice versa, unless stated otherwise):

1.1 "Affiliate" shall mean, with respect to each party, any corporation or other form of business organization, which directly or indirectly owns, controls, is controlled by, or is under common control with, such party. An entity shall be regarded as being in control of another entity if the former entity has the direct or indirect power to order or cause the direction of the policies of the other entity whether (i) through the ownership of more than fifty percent (50%) in the United States, or thirty percent (30%) or more outside the United States, of the outstanding voting securities (or other ownership interest for a business organization other than a corporation) of that entity; or (ii) by contract, statute, regulation or otherwise.

1.2 "Aggregate Carryover Amount" shall have the meaning given in Section 3.3.

-2-

1.3 "Aggregate Spending Target" shall mean Six Hundred Fourteen Million Dollars (\$614,000,000).

1.4 "Annual Carryover Amount" shall have the meaning given in Section 3.3.

1.5 "Annual Minimum Spending Target" for each Program Year, shall mean the sum of (i) the Program Payment of John Hancock for such Program Year as specified in Section 3.1, (ii) Fifty Million Dollars (\$50,000,000), and (iii) any Annual Carryover Amount for the prior Program Year pursuant to Section 3.3. With respect to the fifth Program Year, the "Annual Minimum Spending Target" shall mean the Annual Carryover Amount for the prior Program Year pursuant to Section 3.3.

1.6 "Annual Research Plan" shall mean, for the Program Years in the Program Term, a reasonably and consistently detailed statement of the objectives, activities, timetable and budget for the Research Program for every Program Year remaining in the Program Term, it being understood that less detail shall be required for Program Years that are not the current Program Year. The first Annual Research Plan is attached as Exhibit 1.6. "Annual Research Plan" shall mean, for those years occurring after the expiration of the Program Term, a reasonably and consistently detailed statement of the objectives, activities, timetable and budget for the Research Program for such year only.

1.7 "Bundled Product" shall have the meaning given in paragraph (b) of the definition of Net Sales.

1.8 "Ceased Program" shall mean at least one year has elapsed since Abbott ceased its directed efforts with respect to the applicable Preclinical Program (FTI Program, ED Program or MMPI Program), meaning that Abbott has eliminated the funding for the established research program identified by a core group of researchers dedicated to the applicable Preclinical Program. The continued existence of a researcher separate and apart from such core group shall not affect the determination that a Preclinical Program has ceased.

1.9 "Combination Product" shall mean any product containing one or more Program Compounds combined as a single pharmaceutical product with one or more other therapeutically active ingredients.

1.10 "Commercially Reasonable Efforts" shall mean efforts which are consistent with those normally used by other pharmaceutical companies with respect to other pharmaceutical compounds or products which are of comparable potential commercial value and market potential at a similar stage of development or product life, taking into account, without limitation, issues of safety and efficacy, compound or product profile, proprietary status, the regulatory environment and the status of the compound or product and other relevant scientific factors.

1.11 "Compound Reports" shall have the meaning given in Section 12.2(i).

-3-

1.12 "Confidential Information" shall have the meaning given in Section 10.2.

1.13 "Delivery System Product" shall have the meaning given in paragraph (d) of the definition of Net Sales.

1.14 "Dollars" or "\$" shall mean United States dollars.

1.15 "ED Program" shall mean all of Abbott's discovery efforts to identify compounds (including the identification of pre-clinical and development compounds owned by third parties) which modulate dopamine receptors for the purpose of treating erectile dysfunction.

1.16 "Eisai Agreement" shall mean the License Agreement dated June 29, 2000 between Eisai Co., Ltd. and Abbott related to the Program Compound known as ABT-751.

1.17 "Eisai Territory" shall mean the countries listed on Exhibit 1.17 hereto.

1.18 "Execution Date" shall mean the date set forth in the introductory paragraph to this Agreement.

1.19 [Intentionally Omitted.]

1.20 "FDA" shall mean the U.S. Food and Drug Administration or any successor entity thereto.

1.21 "First Commercial Sale" shall mean the first sale of a Product in a given country by Abbott, its Affiliates or Licensees to an unaffiliated third person after Regulatory Approval has been granted in such country.

1.22 "FTI Program" shall mean all of Abbott's discovery efforts to identify compounds (including the identification of pre-clinical and development compounds owned by third parties) which act as farnesyl transferase inhibitors for the purpose of treating cancer.

1.23 "In-License Agreements" shall mean the Eisai Agreement, the Wakunaga Agreement and the Taisho Agreement.

1.24 "International Territory" shall mean all areas of the world outside the U.S. Territory.

1.25 "Investigational New Drug Application" shall mean an investigational new drug application filed with the FDA in order to commence human clinical testing of a drug in the United States.

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-4-

1.26 "Licensee" shall mean any party licensed or otherwise authorized in writing by Abbott, its Affiliates or its licensees to market, distribute or sell Products and from whom Abbott receives a royalty or other payment based upon sales of Products by such party, its affiliates or its licensees (it being understood that a party that is a merely a distributor, wholesaler or similar reseller of Products is not a Licensee hereunder). In no case shall Eisai Co., Ltd. or Taisho Pharmaceutical Co., Ltd. be considered Licensees under the terms of the Eisai Agreement or Taisho Co-Development Agreement with respect to the Eisai Territory or Japan, respectively.

1.27 "Losses" shall mean any claims, demands, liabilities, costs, damages, judgments, settlements and other reasonable expenses (including attorneys' fees).

1.28 "Milestone Payment" shall have the meaning given in Section 6.3.

1.29 "MMPI Program" shall mean all of Abbott's discovery efforts to identify compounds (including the identification of pre-clinical and development compounds owned by third parties) that inhibit matrix metalloproteinase and treat cancer.

1.30 "NDA" shall mean a New Drug Application (as defined by the FDA) filed with the FDA for the purpose of obtaining Regulatory Approval of a Product in the U.S. Territory.

1.31 "Net Sales" shall mean:

- (a) the total gross sales of the Products (or, for purposes of clauses (b) and (c), the Bundled Products and Combination Products), in each case as set forth on the invoices for such sales by Abbott, its Affiliates and Licensees to unaffiliated third parties in any given period, plus, if applicable, the fair market value of all properties and services received in consideration of a sale of the Products (or, for purposes of clauses (b) and (c), the Bundled Products and Combination Products) by Abbott, its Affiliates and Licensees to unaffiliated third parties during such period, less the following deductions directly paid or actually incurred by Abbott, its Affiliates or Licensees during such period with respect to the sale of the Products (or, for purposes of clauses (b) and (c), the Bundled Products and Combination Products) to the extent included in the gross invoiced sales price therefor:
 - (i) discounts, credits, rebates, allowances, adjustments, rejections, recalls and returns;
 - (ii) price reductions or rebates, retroactive or otherwise, imposed by government authorities;
 - (iii) sales, excise, turnover, inventory, value-added and similar taxes assessed on the royalty-bearing sale of Products;

-5-

- (iv) transportation, importation, insurance and other handling expenses directly chargeable to the royalty-bearing sale of Products;
 - (v) charge backs granted to unaffiliated drug wholesalers; and
 - (vi) the portion of management fees paid to unaffiliated group purchasing organizations that relate specifically to the royalty-bearing sale of Products.
- (b) With respect to a Product which is sold together with any other products and/or services in a country at a unit price, whether packaged together or separately (a "Bundled Product"), the Net Sales of such Bundled Product shall first be calculated in accordance with the definition of Net Sales under paragraph (a), and then the Net Sales of such Bundled Product shall be determined on a country-by-country basis as follows:
- (i) multiply the Net Sales of such Bundled Product in such country by the fraction $A/(A+B)$ where A is the average selling price of such Product in such country when sold separately and B is the total of the average selling prices in such country of each such other product(s) and/or service(s) in such Bundled Product when sold separately; or
 - (ii) if (x) either the average selling price of such Product or the total of the average selling prices of each such other products and/or services in such Bundled Product in such country is not available as of such date or (y) such Product is not sold separately in such country, multiply the Net Sales of such Bundled Product in such country by a percentage determined by the mutual agreement of the Parties which represents the proportionate economic value in such country of such Product relative to the economic value in such country contributed by the other products and/or services in such Bundled Product.
- (c) With respect to a Combination Product, the Net Sales of such Combination Product shall first be calculated in accordance with the definition of Net Sales under paragraph (a), and then the Net Sales of such Combination Product shall be determined on a country-by-country basis as follows:
- (i) multiply the Net Sales of such Combination Product in such country by the fraction $A/(A+B)$, where A is the total of the average selling prices of the Program Compounds in such

-6-

Combination Product when sold separately in such country and B is the total of the average selling prices of each other therapeutically active ingredient when sold alone as a pharmaceutical product in such country; or

- (ii) if (x) either the average selling price of all Program Compounds in such Combination Product or the total of the average selling prices of each other therapeutically active ingredient in such Combination Product in such country is not available or (y) such Program Compounds are not sold separately in such country, multiply the Net Sales of such Combination Product by a percentage determined by mutual agreement of the Parties, which represents the proportionate economic value in such country of all Program Compounds in such Combination Product relative to the economic value in such country contributed by all other therapeutically active ingredients in such Combination Product.
- (d) For purposes of this paragraph (d), a "Premium Delivery System" means any delivery system comprising device(s), equipment, instrumentation or other non-ingestible components (but not solely containers or packaging) designed to assist in the administration of a Product, such as the Abbott ADD-Vantage® System. With respect to a Product which is sold together with a Premium Delivery System (a "Delivery System Product") in a country at a unit price, the Net Sales of such Delivery System Product shall first be calculated in accordance with the definition of Net Sales under paragraph (a), and then the Net Sales of such Product shall be determined on a country-by-country basis as follows:
 - (i) if the Product is sold separately without the Premium Delivery System in a country, reduce the Net Sales of such Delivery System Product in such country by the amount that the average selling price of the Delivery System Product in such country exceeds the average selling price of such Product as sold separately in such country; or
 - (ii) if the Product is not sold separately without the Premium Delivery System in such country, reduce Net Sales of such Delivery System Product by an amount, determined by mutual agreement of the Parties, which represents the proportionate economic value in such country added by the Premium Delivery System.
- (e) Net Sales shall not include any sales of Products containing one Program Compound (and no other Program Compound) known as (i) ABT-751 by Eisai Co. Ltd., its affiliates or licensees in the Eisai Territory or (ii) ABT-

-7-

773 by Taisho Pharmaceutical Co., Ltd., its affiliates or licensees in Japan. Notwithstanding the foregoing sentence, Net Sales shall include in all instances sales by such parties of such products that are outside such territories, respectively.

1.32 "Parties" shall mean Abbott and John Hancock.

1.33 "Patents" shall have the meaning set forth in Section 12.2(e).

1.34 "Phase I Clinical Trial" shall mean a clinical trial of a Program Compound which utilizes a limited number of human beings preliminarily to address safety and to determine what doses can be safely tolerated.

1.35 "Phase II Clinical Trial" shall mean a controlled clinical trial, the primary objective of which is to ascertain additional data regarding the safety and tolerance of one of the Program Compounds and preliminary data regarding such Program Compound's efficacy.

1.36 "Phase III Clinical Trial" shall mean one or a series of controlled pivotal studies of a specific Program Compound by administration of such Program Compound to human beings where the principal purpose of such trial is to provide confirmatory safety and efficacy data necessary to support the filing for Regulatory Approval of a Product.

1.37 "Preclinical Programs" shall mean the following preclinical and clinical programs with potential backup compounds in accordance with Section 4.3(a): the FTI Program, the ED Program and the MMPI Program.

1.38 "Premium Delivery System" shall have the meaning given in paragraph (d) of the definition of Net Sales.

1.39 "Product" shall mean any product containing one or more of the Program Compounds as an active ingredient, alone or in combination with other active ingredients (including any Bundled Product and any Combination Product).

1.40 "Program Compounds" shall mean (i) the compounds listed on Exhibit 1.40; (ii) the first compound (the selection of which shall be consistent with Abbott using Commercially Reasonable Efforts) from each of the Preclinical Programs to enter Phase I Clinical Trial; (iii) any compounds or products substituted or added by Section 4.3; (iv) all line extensions and formulations of the foregoing; and (v) all analogs, isomers, improvements, derivatives and modifications of the foregoing unless such analog, isomer, improvement, derivative or modification would be considered a new chemical entity and required by the FDA to reenter Phase I Clinical Trial. A compound or product shall be considered a Program Compound regardless of the indication for which it is used.

1.41 "Program Inventions" shall have the meaning given in Section 5.1.

-8-

1.42 "Program Payments" shall have the meaning given in Section 3.1.

1.43 "Program Related Costs" shall mean (i) all direct and indirect costs and expenses that are incurred by Abbott on the Research Program during a given Program Year and allocated in a manner consistent with Abbott's internal, pharmaceutical products division-wide allocation procedures; and (ii) the milestone and license fees paid during a given Program Year or during any extension period of the Program Term by Abbott to (a) Eisai Co. Ltd. (not to exceed Eighteen Million Dollars (\$18,000,000) in the aggregate with respect to the Program Compound known as ABT-751 pursuant to the Eisai Agreement) and (b) Wakunaga Pharmaceutical Co., Ltd. (not to exceed Twenty Seven Million Five Hundred Thousand Dollars (\$27,500,000) in the aggregate with respect to the Program Compound known as ABT-492 pursuant to the Wakunaga Agreement). Any payments made by Abbott to John Hancock pursuant to Sections 6.2 and 6.3(a), (b), (c), (d) and (e) shall constitute Program Related Costs. Any payment made by Abbott to John Hancock pursuant to Section 6.3(f) shall not constitute Program Related Costs. Set forth on Exhibit 1.43 is an example of the calculation of Program Related Costs for a particular Program Compound.

1.44 "Program Term" shall mean a period of four (4) consecutive Program Years.

1.45 "Program Year" shall mean a period of twelve (12) consecutive calendar months commencing on January 1 of each year, except that the first Program Year shall commence on the Execution Date and end on December 31, 2001.

1.46 "Quarterly Reporting Period" shall mean the calendar quarter with respect to the U.S. Territory together with the fiscal quarter ending on the final day of February, May, August and November (as the case may be) with respect to the International Territory. For example, the Quarterly Reporting Period that comprises the second calendar quarter with respect to the U.S. Territory also includes the period from March 1 through May 31 with respect to the International Territory. If Abbott adopts the calendar year as its fiscal year for the International Territory, then the Quarterly Reporting Period for the International Territory shall also be the calendar quarter.

1.47 "Research Program" shall mean all of Abbott's, its Affiliates' and Subcontractors' activities directed towards obtaining Regulatory Approval for the Products, including research, development, safety and efficacy studies, clinical trials, process development, formulation work, regulatory, quality, data collection and analysis and project management.

1.48 "Regulatory Approval" shall mean: (i) with respect to the U.S. Territory, the receipt of approval from the FDA to market a Product in the U.S. Territory; and (ii) with respect to any country in the International Territory, receipt of the governmental approvals required to market a Product in such country, including any pricing and reimbursement authorization required in such country.

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-9-

1.49 "Replacement Compound" shall mean a compound (i) made available to Abbott as a result of any transaction involving Abbott or its Affiliates (whether by merger, acquisition or sale of assets or equity, or by license or otherwise), (ii) used for the same class of indications as the Ceased Compound (for example, anti-infectives, cancer, cardiovascular or pain), and (iii) having at least the current and projected potential commercial value to John Hancock as the Ceased Compound.

1.50 "Royalty Term" shall mean, with respect to each Product in each country, a period of ten (10) years from the later of (x) the date of First Commercial Sale of such Product in such country and (y) the two year anniversary of the Execution Date; provided that (i) the obligation to make royalty payments on the Product shall not begin until the two-year anniversary of the Execution Date (and only with respect to Net Sales occurring on or after such date) and (ii) Abbott's obligation to make royalty payments shall cease on December 31, 2015.

1.51 "Subcontractor" shall have the meaning given in Section 2.4.

1.52 "Taisho Agreement" shall mean the Co-Development Agreement dated September 30, 1997 between Taisho Pharmaceutical Co., Ltd. and Abbott related to the Program Compound known as ABT-773.

1.53 "Territory" shall mean both the U.S. Territory and the International Territory, excluding the Eisai Territory with respect to the Program Compound known as ABT-751.

1.54 "U.S. Territory" shall mean the United States of America, excluding Puerto Rico and the U.S. Virgin Islands.

1.55 "Wakunaga Agreement" shall mean the License Agreement dated December 1, 1999 between Wakunaga Pharmaceutical Co., Ltd. and Abbott related to the Program Compound known as ABT-492.

ARTICLE 2 ANNUAL RESEARCH PROGRAM

2.1 Research Program Term. The Research Program shall be conducted by Abbott during the Program Term, and beyond the Program Term until Abbott either abandons development in accordance with the terms hereof or receives Regulatory Approval for each Program Compound, or some combination thereof.

2.2 Research Plan. The Research Program shall be conducted by Abbott in each Program Year in accordance with the Annual Research Plan for such Program Year. The Annual Research Plan will be provided to John Hancock until Abbott either abandons development in accordance with the terms hereof, or receives Regulatory Approval for, each Program Compound in the U.S. Territory, or some combination thereof. The Annual Research Plan shall be prepared

-10-

by Abbott and presented to John Hancock at least forty-five (45) days prior to the start of each Program Year. The first Annual Research Plan is attached as Exhibit 1.6. Abbott may modify the Annual Research Plan from time to time in order to best meet the objectives of the Research Program. Any such modifications to the Annual Research Plan shall be promptly provided to John Hancock. In addition, Abbott shall provide an Annual Research Plan for each year after the end of the Program Term as long as there is an active research program for any Program Compounds.

2.3 Conduct of Research. Abbott shall use Commercially Reasonable Efforts to conduct the Research Program in good scientific manner and using good laboratory practices, to achieve the objectives of the Research Program efficiently and expeditiously and to comply with all applicable laws and regulations. Notwithstanding anything in this Agreement to the contrary, Abbott does not represent, warrant or guarantee that the Research Program will be successful in whole or in part or result in the registration or commercialization of any pharmaceutical products or that any Products obtaining Regulatory Approval will be a commercial success.

2.4 Subcontracting Research. Abbott may subcontract or outsource to Affiliates or third persons (each, a "Subcontractor") any portion of the Annual Research Plan. Consistent with Abbott's past practices, each Subcontractor shall enter into a confidentiality agreement with Abbott and agreements pursuant to which such Subcontractor is required to comply with all applicable laws and regulations, including conducting the Research Program in good scientific manner and using good laboratory practices, with respect to its work on the Research Program. Abbott shall supervise and be responsible under this Agreement for the work of each such Subcontractor on the Research Program and no subcontracting or outsourcing shall relieve Abbott of any of its obligations hereunder.

2.5 Research Reports and Records. Abbott shall, no later than thirty (30) days before the last day of each Program Year, provide John Hancock with a reasonably detailed report setting forth the status of the Research Program and all Program Related Costs expended by Abbott during such Program Year. The Program Related Costs set forth in such report may include good faith estimates with respect to the last three (3) months of the Program Year, provided that the report under this Section 2.5 for the following Program Year contains the actual Program Related Costs for that three (3) month period. Such report shall also contain such other information related thereto as John Hancock may reasonably request from time to time. Abbott shall, and shall cause each Subcontractor to, maintain complete and accurate records, in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes and for purposes of demonstrating compliance with the terms hereof, that fully and properly reflect all work done, results achieved and Program Related Costs expended in performance of the Research Program. The books and records of Abbott and each Subcontractor related to the Research Program, including, without limitation, those related to the expenditure of Program Related Costs, shall be subject to copying, inspection and audit by (and at the expense of) John Hancock at any time and from time to time. Such audit shall occur upon reasonable notice and during normal business hours by an independent auditor selected by John Hancock and reasonably acceptable to Abbott. John Hancock and its independent auditor shall maintain such

-11-

records and information of Abbott in confidence in accordance with Article 10 and shall not use such records or information except to the extent permitted by this Agreement, including any enforcement of the provisions hereof. In the event that such audit reveals any material breach of Abbott's responsibilities hereunder, Abbott shall (i) pay the reasonable fees and expenses charged by such auditor, and (ii) fully and promptly cure such breach.

ARTICLE 3 RESEARCH FUNDING

3.1 John Hancock Program Payments. John Hancock shall make the following installment payments on the applicable payment date (the "Payment Date"), for the applicable Program Year, to Abbott to help support the Research Program (the "Program Payments"):

<u>Payment Date</u>	<u>Amount</u>	<u>Program Year</u>
December 1, 2001	\$50,000,000	First
December 1, 2002	\$54,000,000	Second
December 1, 2003	\$58,000,000	Third
December 1, 2004	\$52,000,000	Fourth

All Program Payments shall be expended by Abbott on Program Related Costs and for no other purpose. If John Hancock has not received at least thirty (30) days prior to the Payment Date both (i) the Annual Research Plan for such year and (ii) the report described in Section 2.5 for the previous Program Year, then John Hancock's obligation to make the Program Payment due on such Payment Date shall be suspended until thirty (30) days have elapsed from the date of John Hancock's receipt of both such Annual Research Plan and report.

3.2 Abbott Funding Obligation. Abbott shall spend on Program Related Costs: (i) during each Program Year, at least the Annual Minimum Spending Target for such Program Year and (ii) at least the Aggregate Spending Target during the Program Term. John Hancock's sole and exclusive remedies for Abbott's failure to fund the Research Program in accordance with this Section 3.2 (but not for any other breach of Abbott's other obligations hereunder) are set forth in Sections 3.3 and 3.4.

3.3 Carryover Provisions. Abbott shall be permitted to change its funding obligations under Section 3.2 only as follows:

- (a) If in any Program Year Abbott spends on Program Related Costs, the full amount of the Program Payment provided by John Hancock for such Program Year, but does not spend the full amount of the Annual Minimum Spending Target for such Program Year (including any Annual Carryover Amounts from any prior Program Years), Abbott will spend on Program Related Costs the difference between its expenditure on Program Related Costs for such Program Year and the Annual Minimum Spending Target

-12-

for such Program Year (the "Annual Carryover Amount") in the subsequent Program Year. John Hancock's obligation to make any Program Payment for such subsequent Program Year, if any, pursuant to Section 3.1, shall be deferred until the time that Abbott has spent and notifies John Hancock that it has spent the Annual Carryover Amount in such subsequent Program Year; and

- (b) If Abbott does not expend on Program Related Costs the full amount of the Aggregate Spending Target during the Program Term, Abbott will expend the difference between its expenditures for Program Related Costs during the Program Term and the Aggregate Spending Target (the "Aggregate Carryover Amount") on Program Related Costs during the subsequent year commencing immediately after the end of the Program Term. If Abbott does not spend the Aggregate Carryover Amount on Program Related Costs during such subsequent year, Abbott will pay to John Hancock one-third of the Aggregate Carryover Amount that remains unspent by Abbott, within thirty (30) days after the end of such subsequent year.

3.4 Termination of John Hancock's Program Payment Obligation. If Abbott: (i) abandons development of all Preclinical Programs and Program Compounds in any Program Year during the Program Term (it being understood that such abandonment need not occur entirely in one Program Year); (ii) does not expend on Program Related Costs during any Program Year the full amount of the Program Payment made by John Hancock for such Program Year; (iii) does not reasonably demonstrate in its Annual Research Plan, its intent and reasonable expectation to expend on Program Related Costs during the next Program Year an amount in excess of the Program Payment to be provided by John Hancock for such year; or (iv) does not reasonably demonstrate in its Annual Research Plan its intent and reasonable expectation to expend on Program Related Costs during the Program Term an amount in excess of the Aggregate Spending Target, John Hancock's obligation to make any remaining Program Payments for any succeeding Program Years pursuant to Section 3.1 shall terminate. For the avoidance of doubt, the Program Payments for the Program Year in which such event occurs shall still be due and payable, adjusted only as set forth in the next sentence, if applicable. In addition, in the case of either (i) or (ii) above, Abbott shall (not later than the 10th day following such event) pay to John Hancock (x) the amount, if any, by which the Program Payment made by John Hancock for such year (in the case of (i) above meaning the Program Year in which all Preclinical Programs and Program Compounds were finally abandoned), if any, exceeds one-half of the Program Related Costs actually spent by Abbott during that Program Year and (y) such additional amount that, after giving effect to the payments referred to in this sentence, causes the Program Related Costs for all years in the Program Term to date to have been funded one-third (1/3) by John Hancock and two-thirds (2/3) by Abbott.

3.5 Hancock Funding Obligation. John Hancock's entire obligation hereunder shall be limited to providing the Program Payments set forth in Section 3.1. Abbott shall be solely

-13-

responsible for funding all Program Related Costs in excess of the Program Payments from John Hancock.

ARTICLE 4 PRODUCT RESEARCH AND DEVELOPMENT

4.1 Commercially Reasonable Efforts. Abbott shall be solely responsible for the clinical development, government approval, manufacturing, marketing, sales and distribution of Products. Abbott will use, and will cause each of its Affiliates and Licensees to use, Commercially Reasonable Efforts to pursue the clinical development, government approval, manufacturing, marketing, sales and distribution of Products throughout the Territory. The obligations of Abbott, its Affiliates and Licensees with respect to any Product under this Article 4 are expressly conditioned upon the safety, efficacy and commercial feasibility of each Product, consistent with using Commercially Reasonable Efforts, but no license, assignment or other transfer of rights by Abbott will modify or reduce Abbott's obligations hereunder (except as set forth in Article 14). It is the parties' expectation that under normal circumstances Abbott will file for Regulatory Approval with respect to each Product in Europe within two (2) years from the date of the NDA filing for such Product in the U.S. Territory and in Japan within five (5) years from such NDA filing date; provided, however, that these time frames may be extended or otherwise altered based upon unforeseen circumstances that legitimately impact such regulatory filings in such foreign jurisdictions.

4.2 Marketing and Sale Responsibility. Without limiting the generality of Section 4.1, within six (6) months of obtaining Regulatory Approval for a Product in a given country, Abbott, its Affiliates or Licensees shall commence to market and sell such Product in such country. Abbott's obligation to market and sell a Product shall not apply to a Product in any country if Abbott has not commenced or has ceased marketing and selling such Product in such country substantially on account of adverse business or financial conditions caused by the regulatory authorities or other governmental authorities of such country (including not commencing marketing and selling in a country where the regulatory authorities have price or reimbursement approval and the price or reimbursement approval or that proposed by the regulatory authorities or government authorities is unacceptable to Abbott) which causes the marketing and sale of such Product in such country to be contrary to the financial best interests of John Hancock and Abbott; provided, however, that Abbott, its Affiliates or Licensees shall commence or resume marketing and sale of such Product in such country as soon as reasonably practical after such adverse business or financial conditions cease to exist.

4.3 Failure of Program Compound to Progress.

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JH 008093

- (a) Preclinical Programs: ED Program, FTI Program and MMPI Program.
With respect to any Program Compound resulting from a Preclinical Program that Abbott ceases to develop past Phase I Clinical Trial (i.e., does not enter a Phase II Clinical Trial) (a "Failed Early Stage Program

-14-

Compound"), for which Abbott or its Affiliates has or will have one or more other compounds in such respective Preclinical Program (which includes all in-licensed compounds not yet approved for marketing), the next compound to enter Phase I Clinical Trials from such Preclinical Program shall be considered a Program Compound in all respects hereunder, as of the date of the cessation of such Failed Early Stage Program Compound; provided however, with respect to each Preclinical Program, there shall be no more than three Program Compounds substituted under this Section 4.3(a) (for an aggregate maximum of nine (9) such substitutions for all Preclinical Programs). At the time a Preclinical Program becomes a Ceased Program, Abbott shall have no further obligation to provide a substitute for a Failed Early Stage Program Compound.

- (b) Failure of ABT-492 or ABT-510 to Yield a Compound that Enters a Phase II Clinical Trial. If (i) ABT-492 fails to enter a Phase II Clinical Trial, or (ii) ABT-510 fails to enter a Phase II Clinical Trial, then within six (6) months after the failure of the first such Program Compound to enter a Phase II Clinical Trial, Abbott shall substitute a compound in a Phase II Clinical Trial having a commercial value not less than that currently expected for ABT-492 and ABT-510, respectively (as of the date of execution of this Agreement).
- (c) Cessation as a Result of an Acquired Replacement Compound. If Abbott ceases or substantially ceases developing, marketing or selling any Program Compound (that is in Phase I or beyond) or Product (a "Ceased Compound"), and if such cessation or substantial cessation is a result of Abbott's acquisition of a Replacement Compound, then the Replacement Compound shall be considered a Program Compound and/or Product from the date of such acquisition and the Ceased Compound shall no longer be considered a Program Compound.

In the event that the Replacement Compound has been approved for marketing by the FDA and the Ceased Compound has not been approved for marketing by the FDA as of the date of such acquisition, Section 4.3(d) shall apply and the first paragraph of this Section 4.3(c) shall not apply.

In the event that the Ceased Compound has been approved for marketing by the FDA as of the date of such acquisition, John Hancock shall have the option, in its sole discretion, to have Abbott maximize the commercial value of the Ceased Compound pursuant to Section 4.3(d) instead of having the Ceased Compound be subject to this Section 4.3(c).

CONFIDENTIAL
JH 008094

-15-

- (d) Cessation for Reasons Other than Section 4.3(c). If a Program Compound (that is in Phase I or beyond) or Product becomes a Ceased Compound for any reason not as a result of the acquisition of a Replacement Compound as set forth in Section 4.3(c) above and provided that such Ceased Compound has commercial value, then
- (i) as soon as is practicable Abbott shall maximize the commercial value, if any, of the Ceased Compound to both parties by out-licensing or divesting such Ceased Compound to a third party; provided, however, if the out-licensing or divestiture of such Ceased Compound requires the approval of Taisho Pharmaceutical Co., Ltd. (in the case of Program Compound ABT-773), Eisai Co., Ltd. (in the case of Program Compound ABT-751) or Wakunaga Pharmaceutical Co., Ltd. (in the case of Program Compound ABT-492), pursuant to the respective In-License Agreement, and such entity does not grant such approval, then Abbott shall within a reasonable period of time but not more than three months substitute a compound (which shall thereupon become a "Program Compound") having at least the current and projected potential commercial value as such Ceased Compound;
 - (ii) John Hancock shall be permitted (but have no obligation) to assist in such out-license and/or divestiture effort; and
 - (iii) Abbott shall remunerate John Hancock based on the sales of such Ceased Compound by the third party that has acquired or licensed the Ceased Compound (the "Acquirer") in a manner most consistent with the allocation that would have applied hereunder had such Ceased Compound not been so out-licensed or divested, i.e., in accordance with the royalties and milestones payable hereunder. The appropriate royalty rate payable to John Hancock shall be determined by adding the Acquirer's Net Sales of the Ceased Compound to the total Net Sales of other Products.
- (e) Divestiture. Notwithstanding anything herein to the contrary, Abbott shall not divest or out-license any Program Compound (which shall mean a sale, license or other transfer by Abbott of the right to develop, market and sell any Product containing such Program Compound either (i) in all of North America or (ii) in the countries of Japan and/or the European Union that have at least two-thirds of the total population of Japan and the European Union), without John Hancock's prior written consent, which consent shall not be unreasonably withheld; provided however, if such Program Compound is being divested as a result of direction from the

-16-

Federal Trade Commission to so divest, John Hancock's written consent shall not be required.

- (f) Notice and Information. Abbott shall promptly notify John Hancock upon occurrence of any decision by Abbott to cease or substantially cease developing, marketing or selling any Program Compound or Product. In addition, Abbott shall provide to John Hancock all information reasonably requested by John Hancock related to any Replacement Compound, Program Compound, or Product that is subject to the provisions of this Section 4.3.
- (g) Commercially Reasonable Efforts. Nothing in this Section 4.3 shall lessen any of Abbott's other obligations under this Agreement nor permit Abbott to perform in any manner that is not clearly consistent with using its Commercially Reasonable Efforts hereunder.

4.4 Arm's-Length. Abbott shall not research, develop, manufacture, market, sell, distribute, out-license or otherwise treat any Program Compounds or Products differently, as compared to any other Abbott compounds or products, on account of any of John Hancock's rights hereunder. Furthermore, all distribution agreements, licenses; out-licenses and other agreements relating to the research, development, manufacturing, marketing, sale, distribution, licensing, out-licensing or divestiture of and all other transactions involving any Program Compounds or Products to or with any third party (except to Abbott's Affiliates) shall be on arm's-length terms and conditions.

4.5 In-License Agreements. Abbott shall comply in all material respects with the terms and conditions of the In-License Agreements. Abbott shall not amend the In-License Agreements or waive any of its rights thereunder without John Hancock's prior written consent (such consent not to be unreasonably withheld), unless such amendment or waiver does not have and would not have a material adverse effect on John Hancock's interests hereunder. To the extent that Abbott or any of its Affiliates obtains the right to market, distribute or sell Products containing the Program Compound known as ABT-751 in the Eisai Territory, then sales by Abbott, its Affiliates and Licensees of such Products in such territory shall be included in all respects hereunder (including without limitation in Net Sales and the Territory).

ARTICLE 5 PROGRAM INVENTIONS

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JH 008096

5.1 Ownership. As between Abbott and John Hancock, all inventions, innovations, ideas, discoveries, technology, know-how, methods, data, applications and products (in each case whether or not patentable) arising from the Research Program or otherwise related to the Program Compounds (collectively, the "Program Inventions") shall be exclusively owned by or assigned to Abbott. Abbott shall not divest, out-license or otherwise transfer any of its right, title

-17-

or interest in or to any Program Inventions which would prevent or impair Abbott's ability to fulfill its obligations to John Hancock under this Agreement.

5.2 Patent Prosecution and Maintenance. To the extent it owns a Program Invention or has the contractual right to pursue patent protection for a Program Invention, Abbott will use Commercially Reasonable Efforts to obtain patent protection for the Program Inventions in the Territory. As between Abbott and John Hancock, Abbott shall be responsible for all costs and expenses and control all decisions related to pursuing such patent protection, including the preparation, filing (foreign and/or domestic), prosecution, issuance and maintenance of patent applications or patents covering Program Inventions.

5.3 Enforcement. As between Abbott and John Hancock, Abbott shall have the sole right and authority to enforce the patents or any other rights arising from the Program Inventions (including without limitation the Patents) against any infringers. If Abbott initiates any action or lawsuit to enforce such patents or other rights, it shall be solely responsible for the cost and expense thereof. Abbott will promptly notify John Hancock at such time as it becomes aware of any infringement activities and of any such enforcement actions or lawsuit, and Abbott will provide information concerning them as reasonably requested by John Hancock. All moneys recovered upon the final judgment or settlement of any such action or lawsuit, less the out-of-pocket cost and expense thereof, shall be allocated between Abbott and John Hancock proportional to Abbott's lost profits and John Hancock's lost royalties as a result of such infringement.

ARTICLE 6

MILESTONE PAYMENTS TO JOHN HANCOCK

6.1 [Intentionally omitted].

6.2 Management Fee. On December 1, 2002, 2003 and 2004, Abbott shall pay to John Hancock a management fee, each of which shall be in the amount of Two Million Dollars (\$2,000,000).

6.3 Milestone Notification and Payments. Abbott shall promptly notify John Hancock of the occurrence any of the following events that give rise to Abbott's obligation to make a payment pursuant to this Section 6.3 (each, a "Milestone Payment"). Except as hereinafter limited, Abbott shall pay the following Milestone Payments to John Hancock in the amounts and at the times set forth below with respect to each Program Compound:

- (a) One Million Dollars (\$1,000,000) shall be paid within thirty (30) days after the allowance by the FDA of each Investigational New Drug Application for such Program Compound;

CONFIDENTIAL
JH 008097

-18-

- (b) Two Million Dollars (\$2,000,000) shall be paid within thirty (30) days after the initiation of each Phase I Clinical Trial with such Program Compound;
- (c) Three Million Dollars (\$3,000,000) shall be paid within thirty (30) days after the initiation of each Phase II Clinical Trial with such Program Compound;
- (d) Four Million Dollars (\$4,000,000) shall be paid within thirty (30) days after the initiation of each Phase III Clinical Trial with such Program Compound; and
- (e) Five Million Dollars (\$5,000,000) shall be paid within thirty (30) days after the filing of each NDA with the FDA for such Program Compound.

In addition, except as hereinafter limited, Abbott shall pay the following Milestone Payments to John Hancock in the amounts and at the times set forth below:

- (f) (i) Twenty Million Dollars (\$20,000,000) shall be paid within thirty (30) days after the Regulatory Approval of the first Product in the U.S. Territory;
- (ii) Ten Million Dollars (\$10,000,000) shall be paid within thirty (30) days after the Regulatory Approval of the second Product in the U.S. Territory; and
- (iii) Ten Million Dollars (\$10,000,000) shall be paid within thirty (30) days after the Regulatory Approval of third Product in the U.S. Territory.

The aggregate of Milestone Payments under Section 6.3(a), (b), (c), (d), and (e) for all Program Compounds shall be limited to Eight Million Dollars (\$8,000,000), and once such aggregate limit has been paid, no further payments shall be due and payable under Sections 6.3(a), (b), (c), (d) or (e).

The aggregate of Milestone Payments under Sections 6.3(a), (b), (c), (d) and (e) for all Program Compounds shall be limited to zero dollars (\$0) during the first Program Year, Two Million Dollars (\$2,000,000) during the second Program Year, and Six Million Dollars (\$6,000,000) during the third Program Year, and once such annual limit has been reached for these particular Program Years, no further payments shall be due under Sections 6.3(a), (b), (c), (d) and (e) for the remainder of such Program Year; provided that any amounts that would have been due to John Hancock but for such annual limits shall be paid in subsequent Program Years so long as the Program Compound to which it relates has not been abandoned, divested or out-licensed by Abbott, subject to the Eight Million Dollar (\$8,000,000) limitation set forth above. Subject to

-19-

the limitations above, the Milestone Payments under Sections 6.3(a), (b), (c), (d) and (e) may be made more than once with respect to each Program Compound.

The aggregate of Milestone Payments under Section 6.3(f) for all Program Compounds shall be limited to Forty Million Dollars (\$40,000,000), and once such aggregate limit has been paid, no further payments shall be due and payable under Section 6.3(f). In addition, Milestone Payments under Section 6.3(f) shall not be paid more than once for any particular Program Compound.

Exhibit 1.40 sets forth the current stage of clinical development for each Program Compound.

ARTICLE 7 ROYALTIES

7.1 Royalty Rates. Subject to the limitation set forth below, Abbott shall pay to John Hancock royalties equal to the following percentages of Net Sales, aggregated on a yearly basis, of all Products in the Territory:

<u>Royalty percentage</u>	<u>Yearly Net Sales (in millions) of all Products in the Territory</u>
8.5% of those Net Sales	up to \$400
and then 4% of those Net Sales	in excess of \$400 up to \$1,000
and then 1% of those Net Sales	in excess of \$1,000 up to \$2,000
and then 0.5% of those Net Sales	in excess of \$2,000

Net Sales shall be aggregated yearly (i) in the case of the U.S. Territory, on a calendar year basis, together with (ii) in the case of the International Territory, on a December 1 to November 30 basis, in each case consistent with the determination of Quarterly Reporting Periods.

7.2 Royalty Term. The duration of the obligation to make royalty payments on each Product shall be determined on a country-by-country basis and shall last for the duration of the Royalty Term in each given country for such Product.

ARTICLE 8 ROYALTY REPORTS AND ACCOUNTING

8.1 Reports. Exchange Rates. With respect to every Quarterly Reporting Period for which Abbott is obligated to pay any royalty hereunder, Abbott shall furnish to John Hancock a single written report for such Quarterly Reporting Period within sixty (60) days after the end of such Quarterly Reporting Period (that is, within sixty (60) days after each March 31, June 30, September 30 and December 31, as the case may be) showing in reasonably specific detail:

CONFIDENTIAL
JH 008099

-20-

- (a) the total gross sales in each country for each Product sold by Abbott, its Affiliates and Licensees in the Territory and the detailed calculation of Net Sales from gross sales in each country for each Product;
- (b) the royalties payable in Dollars, if any, which shall have accrued hereunder;
- (c) the dates of the First Commercial Sale of each Product in any country in the Territory during such Quarterly Reporting Period; and
- (d) the exchange rates used in determining the amount of Dollars.

With respect to sales of Products invoiced in Dollars, the gross sales, Net Sales (including all adjustments and deductions permitted to be made hereunder in calculating the same), and royalties payable shall be expressed in Dollars. With respect to sales of Products invoiced in a currency other than Dollars, the gross sales, Net Sales (including all adjustments and deductions permitted to be made hereunder in calculating the same) and royalties payable shall be expressed in their Dollar equivalent, calculated using the Inter Bank rate set forth in the International Report published by International Reports Inc. as Foreign Exchange Rates quoted in New York on the day nearest the last business day of the Quarterly Reporting Period.

8.2 Audits.

- (a) Upon the written request of John Hancock and, in the absence of any breach by Abbott hereunder, not more than once in each calendar year, Abbott shall permit John Hancock and an independent certified public accounting firm of nationally recognized standing, selected by John Hancock and reasonably acceptable to Abbott, at John Hancock's expense, to have access during normal business hours to such of the records of Abbott, its Affiliates and Licensees to verify the accuracy of the royalty reports and the amounts and calculation of any payments required hereunder for any year ending not more than five (5) years prior to the date of such request.
- (b) If such accounting firm concludes that additional royalties or other payments were owed during such period, Abbott shall have the option to invoke the proceedings of Section 16.7 below or pay the additional royalties or other payments within thirty (30) days after the date John Hancock delivers to Abbott such accounting firm's written report so concluding. The reasonable fees and expenses charged by such accounting firm shall be paid by John Hancock; provided, however, if the audit discloses that the amounts payable by Abbott for any Quarterly Reporting Period are more than one hundred five percent (105%) of the royalties

-21-

actually paid for such period, then Abbott shall pay the reasonable fees and expenses charged by such accounting firm.

- (c) Abbott shall cause its Affiliates to, and shall include in each license granted by it relating to a Program Compound or Product a provision requiring the Licensee to, (i) make reports to Abbott, (ii) keep and maintain records of Net Sales made pursuant to such license and (iii) grant access to such records by John Hancock and its accounting firm or other auditor to the same extent required of Abbott under this Agreement.
- (d) All reports and payments not disputed as to correctness by John Hancock within five (5) years after receipt thereof shall thereafter conclusively be deemed correct for all purposes, and Abbott, its Affiliates and Licensees shall be released from any liability or accountability with respect to such reports and payments.

8.3 Confidential Financial Information. John Hancock shall treat all information subject to review under this Article 8, and shall cause its accounting firm to agree to treat all such information, in accordance with the provisions of Article 10.

8.4 Accounting Principles. All accounting hereunder, including without limitation all determinations of gross sales, Net Sales (including all adjustments and deductions permitted to be made hereunder in calculating the same), Program Related Costs and all calculations underlying such determinations, shall be made in accordance with generally accepted accounting principles as in effect in the United States, consistently applied.

ARTICLE 9 PAYMENTS

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JH 008101

9.1 Payment Terms. With respect to every Quarterly Reporting Period for which Abbott is obligated to pay a royalty hereunder, such royalties shall be due and payable in a single payment within sixty (60) days of the end of such Quarterly Reporting Period (that is, within sixty (60) days of each March 31, June 30, September 30 and December 31, as the case may be). Payment of royalties may be made in advance of such due date.

9.2 Payment Method. All royalties and other payments by Abbott to John Hancock under this Agreement shall be made by bank wire transfer in immediately available funds in accordance with the instructions set forth on Exhibit 9.2 attached hereto or in accordance with such other instructions as John Hancock may give from time to time.

9.3 Late Payments. Each party shall pay interest to the other on the aggregate amount of any payments by it that are not paid on or before the date such payments are due under this Agreement, including, without limitation, any disputed payments or payments resulting from any

-22-

audit, at a rate per annum equal to the lesser of (a) the prime rate of interest plus two hundred (200) basis points as reported by Citibank, N.A. in New York, from time to time (with any change in such reported rate being effective immediately for purposes hereof), or (b) the highest rate permitted by applicable law, calculated on the number of days such payments is delinquent until paid in full in cash. All such amounts shall be payable upon demand.

ARTICLE 10 CONFIDENTIALITY

10.1 Nondisclosure Obligations. Except as otherwise provided in this Article 10, during the term of the Agreement and for a period of ten (10) years thereafter, (a) John Hancock shall maintain in confidence in accordance with such procedures as are adopted by John Hancock to protect its own confidential information and shall use only for purposes of this Agreement (including, without limitation, enforcement of the terms hereof), information and data related to the Program Compounds or Products; and (b) John Hancock shall also maintain in confidence in accordance with such policies, and use only for purposes of this Agreement, all information and data supplied by Abbott under this Agreement, which if disclosed in writing is marked "confidential", if disclosed orally is promptly thereafter summarized and confirmed in writing to the other party and marked "confidential", or if disclosed in some other form is marked "confidential."

10.2 Permitted Disclosures. For purposes of this Article 10, information and data described in clause (a) or (b) above shall be referred to as "Confidential Information". John Hancock may disclose Confidential Information as required by applicable law, regulation or judicial process, provided that John Hancock shall, if legally permitted, give Abbott prompt written notice thereof. The obligation not to disclose or use Confidential Information shall not apply to any part of such Confidential Information that (i) is or becomes patented, published or otherwise part of the public domain other than by acts or omissions of John Hancock in contravention of this Agreement; or (ii) is disclosed to John Hancock by a third party, provided such Confidential Information was not obtained on a confidential basis by such third party from Abbott, its Affiliates or Licensees; or (iii) prior to disclosure under the Agreement, was already in the possession of John Hancock, provided such Confidential Information was not obtained directly or indirectly from Abbott, its Affiliates or Licensees under an ongoing obligation of confidentiality; or (iv) is disclosed in a press release agreed to by both parties under Section 10.3 below.

10.3 Publicity Review. Without the prior written consent of the other party, neither party shall make any statement to the public regarding the execution and/or any other aspect of the subject matter of this Agreement and John Hancock shall not make any statement to the public regarding any work under the Research Program; provided that, Abbott may make statements to the public regarding work done under the Research Program (without reference to or mention of John Hancock) and the commercialization of any Products resulting therefrom in accordance with its standard business practices. John Hancock and Abbott shall not disclose any

-23-

terms or conditions of this Agreement to any third party without the prior consent of the other party, except as set forth above in this Section 10.3 or as required by applicable law, regulation or court order. The parties agree not to issue a press release announcing the execution of this Agreement.

ARTICLE 11 TERM AND TERMINATION

11.1 Expiration. This Agreement shall expire upon satisfaction of Abbott's obligations to pay royalties under Section 7.2 and all other amounts under this Agreement.

11.2 Termination; Material Breach. It is the parties' express intent that consideration shall be given to remedying any breach of this Agreement through the payment of monetary damages or such other legal or equitable remedies as shall be appropriate under the circumstances and that there shall only be a limited right to terminate this Agreement under the following circumstances.

- (a) In the event that the court, in accordance with the procedures set forth in Section 16.2, has issued a ruling that John Hancock has breached its obligation under Section 3.1 of this Agreement (obligation to make payments), and such ruling specified the actions to be taken by John Hancock on account of such breach, and John Hancock has failed to comply with the terms of such ruling within the time period specified therein for compliance and the time for any appeal has expired without the submission of an appeal, then, in addition to all other rights available to Abbott under law and equity, including its right to enforce such ruling in court, Abbott shall have the right to terminate the Agreement as a result of John Hancock's failure to abide by the terms of this Agreement and such ruling.
- (b) In the event that the court, in accordance with the procedures set forth in Section 16.2, has issued a ruling that Abbott has breached a material obligation under this Agreement, and such ruling specified the actions to be taken by Abbott on account of such breach, and Abbott has failed to comply with the terms of such ruling within the time period specified therein for compliance and the time for any appeal has expired without the submission of an appeal, then, in addition to all other rights available to John Hancock under law and equity, including its right to enforce such ruling in court, John Hancock shall have the right to terminate the Agreement, each as a result of Abbott's failure to abide by the terms of this Agreement and such ruling.

CONFIDENTIAL
JH 008103

-24-

11.3 Effect of Expiration or Termination. Expiration or, if applicable, termination of this Agreement shall not relieve the parties of any obligation accruing prior to such expiration or termination. The provisions of Articles 8 (Royalty Reports and Accounting), 10 (Confidentiality), 11 (Term and Termination), 12 (Warranties and Indemnification) and 16 (Miscellaneous) shall survive the expiration or termination of this Agreement.

ARTICLE 12
WARRANTIES AND INDEMNITY

12.1 John Hancock Representations and Warranties. John Hancock represents and warrants to Abbott that as of the Execution Date:

- (a) The execution and delivery of this Agreement and the performance of the transactions contemplated hereby have been duly authorized by all appropriate John Hancock corporate action. This Agreement constitutes John Hancock's valid and binding legal obligation, enforceable against it in accordance with its terms.
- (b) The performance by John Hancock of any of the terms and conditions of this Agreement on its part to be performed does not and will not constitute a breach or violation of its organizational documents or any other material agreement or understanding, written or oral, to which it is a party or any law, statute, rule or regulation by which it is bound.
- (c) No consent, approval, license or authorization of, or designation, declaration or filing with, any court or governmental authority is or will be required on the part of John Hancock in connection with the execution, delivery and performance by John Hancock of this Agreement or any other agreements or instruments executed and delivered by John Hancock in connection herewith or therewith, including, without limitation, any filings pursuant to federal or state securities laws or pursuant to any federal anti-trust laws.
- (d) Neither John Hancock nor any person acting on its behalf (i) has taken or will take any action which would subject this Agreement and the consummation of the transactions contemplated hereby to the registration or qualification requirements of any federal or state securities laws, (ii) has dealt with any broker, finder or other similar person in connection with the transactions contemplated by this Agreement or (iii) is under any obligation to pay any broker's fee, finder's fee or commission in connection with such transactions.

12.2 Abbott Representations and Warranties. Abbott represents and warrants to John Hancock that as of the Execution Date:

-25-

- (a) The execution and delivery of this Agreement and the performance of the transactions contemplated hereby have been duly authorized by all appropriate Abbott corporate action. This Agreement constitutes Abbott's valid and binding legal obligation, enforceable against it in accordance with its terms.
- (b) The performance by Abbott of any of the terms and conditions of this Agreement on its part to be performed does not and will not constitute a breach or violation of its organizational documents or any other agreement or understanding, written or oral, to which it is a party or any law, statute, rule or regulation by which it is bound.
- (c) No consent, approval, license or authorization of, or designation, declaration or filing with, any court or governmental authority is or will be required on the part of Abbott in connection with the execution, delivery and performance by Abbott of this Agreement or any other agreements or instruments executed and delivered by Abbott in connection herewith or therewith, including, without limitation, any filings pursuant to federal or state securities laws or pursuant to any federal anti-trust laws, except those consents, approvals, licenses, authorizations, and other requirements imposed by governmental authorities (both U.S. and foreign) and such declarations and filings with governmental authorities (both U.S. and foreign) required in the normal course of pharmaceutical research, development, marketing and sale.
- (d) Set forth on Exhibit 12.2(d) is the full name, chemical name, detailed description of the stage of development and current status, for each Program Compound. Set forth on Exhibit 1.6 in each Annual Research Plan is a description of projected milestones and dates thereof, projected year of NDA filing, and projected costs to be incurred by Abbott during the Program Term, for each Program Compound. Such projections were prepared in good faith and with due care based on reasonable assumptions, and represent the reasonable estimate of Abbott based on information available as of the date of such projections and as of the date hereof; it being agreed that such projections do not constitute any warranty as to the future performance of the Program Compounds and that actual results may vary from such projections.
- (e) Set forth on Exhibit 12.2(e) is a list and description of all domestic and foreign patents, patent rights, patent applications and all patent applications that are in the process of being prepared that are owned by or registered in the name of Abbott, or of which Abbott is a licensee or in which Abbott has any right, which claim any of the Program Compounds (the "Patents"). Abbott solely owns all of the Patents, except as indicated

-26-

on Exhibit 12.2(e). All of the material Patents have been duly filed in or issued by the United States Patent and Trademark Office or the equivalent foreign patent office identified on Exhibit 12.2(e), as the case may be, and have been properly maintained and renewed in accordance with all applicable laws and regulations. With respect to the Patents that it does not own, Abbott has an exclusive and valid license thereunder to develop, make, have made, use, market and sell (with the right to sublicense) the applicable Program Compounds in the entire Territory; provided however, (i) with respect to Italy, Abbott has such rights that are co-exclusive with Eisai Co. Ltd. for the Program Compound known as ABT-751 and (ii) with respect to Japan, Abbott has such rights that are co-exclusive with Taisho Pharmaceutical Co., Ltd. for the Program Compound known as ABT-773. Except with respect to the Preclinical Programs, to Abbott's knowledge, it is not necessary to obtain or license any patents, patent rights, inventions, copyrights, manufacturing processes, formulas, trade secrets, proprietary rights or know-how that it does not currently have in order to (i) develop, make, have made, use, market and sell the Program Compounds or (ii) conduct the Research Program as heretofore conducted and as proposed to be conducted. Except with respect to those Program Compounds that are the subject of In-License Agreements, the Program Compounds are owned exclusively by Abbott, free and clear of any liens or encumbrances of any other person and, to Abbott's knowledge, Abbott does not require the consent of any other person to develop, make, have made, use, market and sell the Program Compounds.

- (f) Except as set forth in Exhibit 12.2(f) (but in any event, as of the Execution Date, such matters are not, and could not reasonably be expected to be material), Abbott has not received any communications alleging that, and no claim is pending or, to the knowledge of Abbott, threatened to the effect that, the operations of Abbott with respect to the Research Program or the Program Compounds infringe upon or conflict with (or will infringe or conflict with) the asserted rights of any other person under any domestic or foreign patent, trademark, service mark, copyright, trade secret, proprietary right or any other intellectual property right, and, except for the Preclinical Programs, there is no material basis known to Abbott for any such claim (whether or not pending or threatened). No claim is pending or, to the knowledge of Abbott, threatened to the effect that any of the Patents are invalid or unenforceable by Abbott, and there is no material basis known to Abbott for any such claim (whether or not pending or threatened). The publication of any material technical information with respect to the Program Compounds developed by and belonging to Abbott is subject to review and approval under Abbott's existing procedures.
- (g) Except for the In-License Agreements and customary employment and consulting agreements with Abbott's employees and consultants, there are

-27-

no outstanding options, licenses, or agreements of any kind relating to the Patents or any of the Program Compounds or the transactions contemplated by this Agreement, which license the Patents or any technical information developed in the course of the clinical development program to any third party to register, market or sell any of the Program Compounds or Products.

- (h) To the knowledge of Abbott with respect to the Research Program and each of the Program Compounds, Abbott is not now, and in performing its obligations hereunder will not be, in any way making an unlawful or wrongful use of any confidential information, know-how, or trade secrets of any other person.
- (i) Neither this Agreement nor any Exhibit to this Agreement (including the compound reports attached as Exhibit 12.2(i) hereto (the "Compound Reports") contains any untrue statement of material fact or omits to state any material fact necessary to make the statements contained herein or therein not misleading. There is no fact known to Abbott (other than generally available information concerning the pharmaceutical industry in general) as of the date of this Agreement that has not been disclosed in this Agreement or any Exhibit to this Agreement which has resulted in, or could reasonably be expected to result in, a material adverse effect on the prospects or condition (including safety, efficacy, scientific viability or commercial) of the Research Program or any of the Program Compounds.
- (j) Neither Abbott nor any person acting on its behalf (i) has taken or will take any action which would subject this Agreement and the consummation of the transactions contemplated hereby to the registration or qualification requirements of any federal or state securities laws, (ii) has dealt with any broker, finder or other similar person in connection with the transactions contemplated by this Agreement or (iii) is under any obligation to pay any broker's fee, finder's fee or commission in connection with such transactions.
- (k) Other than generally publicized actions, proceedings or investigations concerning the pharmaceutical industry in general, there is no action, proceeding or investigation pending or, to the knowledge of Abbott, threatened which (i) questions the validity of this Agreement or any action taken or to be taken by Abbott pursuant thereto or (ii) which has resulted in, or could reasonably be expected to result in, a material adverse effect on the prospects or condition (including safety, efficacy, scientific viability or commercial) of the Research Program or any of the Program Compounds.

-28-

- (l) With respect to the Research Program and each of the Program Compounds, Abbott has (and in the future will have) obtained, to the extent permitted by law, from each of its employees, consultants, Affiliates and Subcontractors an agreement that reasonably protects Abbott's interest in the Program Inventions, Program Compounds and Products.
- (m) With respect to each Program Compound, since the date of its respective Compound Report, to the knowledge of Abbott, no condition, circumstance or fact has arisen (other than generally available information concerning the pharmaceutical industry in general) nor has Abbott made any change in the conduct of the Research Program which, individually or in the aggregate, has resulted in, or could reasonably be expected to result in, a material adverse effect on the prospects or condition (including safety, efficacy, scientific viability or commercial) of such Program Compounds.
- (n) Each In-License Agreement is valid, binding and in full force and effect, and there is no event which has occurred or exists, which constitutes or which, with notice and/or the passage of time, would constitute a material default or breach under any such contract by Abbott or, to Abbott's knowledge, any other party thereto, or would cause the acceleration of any obligation of any party thereto or give rise to any right of termination or cancellation thereof. Abbott has no reason to believe that the parties to each In-License Agreement will not fulfill their obligations thereunder in all material respects or that such parties do not have the right to grant the licenses granted thereunder. Abbott has no reason to believe that it will not fulfill its obligations under the In-License Agreements. Under the Eisai Agreement, neither Abbott nor its Affiliates has the right to market, distribute or sell Products containing the Program Compound known as ABT-751 in the Eisai Territory (with the exception of Italy).

12.3 No Conflict. Abbott and John Hancock represent and warrant that this Agreement does not, and will not, conflict with any other right or obligation provided under any other agreement or obligation that Abbott or John Hancock has with or to any third party.

12.4 Compliance with Law. Each party represents and warrants to the other that it will comply with all applicable laws, regulations and guidelines in connection with its performance of its obligations and rights pursuant to this Agreement, including the regulations of the United States and any other relevant nation concerning any export or other transfer of technology, services or products.

12.5 No Other Warranties. EACH PARTY TO THIS AGREEMENT AGREES THAT, EXCEPT FOR THE REPRESENTATIONS AND WARRANTIES CONTAINED IN THIS AGREEMENT, NEITHER PARTY MAKES ANY OTHER REPRESENTATIONS OR

-29-

WARRANTIES, AND EACH HEREBY DISCLAIMS ANY OTHER REPRESENTATIONS OR WARRANTIES MADE BY ITSELF OR ANY OF ITS OFFICERS, DIRECTORS, EMPLOYEES, AGENTS, FINANCIAL AND LEGAL ADVISORS OR OTHER REPRESENTATIVES, WITH RESPECT TO THE EXECUTION AND DELIVERY OF THIS AGREEMENT OR THE TRANSACTIONS CONTEMPLATED BY THIS AGREEMENT, NOTWITHSTANDING THE DELIVERY OR DISCLOSURE TO THE OTHER OR THE OTHER'S REPRESENTATIVES OF ANY DOCUMENTATION OR OTHER INFORMATION WITH RESPECT TO ANY ONE OR MORE OF THE FOREGOING.

12.6 General Indemnification of John Hancock. Abbott shall indemnify and hold John Hancock and its Affiliates, agents, directors and employees harmless, and hereby forever releases and discharges John Hancock and its Affiliates, agents, directors and employees, from and against all Losses related to or arising out of, directly or indirectly, (i) any negligence, recklessness or intentional misconduct of Abbott or its Affiliates, agents, directors, employees, Subcontractors, licensees (including Licensees) or sublicensees in connection with the Research Program, Program Compounds or Products, or (ii) any manufacture, use, storage, distribution or sale of the Program Compounds or Products by anyone, including without limitation all Losses related to any personal injury or death, or (iii) any breach by Abbott of its representations, warranties or obligations hereunder, or (iv) the consummation of the transactions contemplated hereby, except, in each case, to the extent any such Losses are the result of (A) any breach by John Hancock of its representations, warranties or obligations hereunder, or (B) any negligence, recklessness, or intentional misconduct by John Hancock or its Affiliates, agents, directors, employees.

12.7 Indemnification Relating to Certain In-Licensed Compounds. Abbott shall indemnify and hold John Hancock and its Affiliates, agents, directors and employees harmless, and hereby forever releases and discharges John Hancock and its Affiliates, agents, directors and employees, from and against all Losses to the extent related to or arising out of, directly or indirectly, the fact that Abbott's rights in the Program Compounds known as ABT-773, ABT-492 and ABT-751 and the Patents and other patent rights, copyrights, trade secret rights and other intellectual property rights related thereto arise from the Taisho Agreement, the Wakunaga Agreement or the Eisai Agreement respectively, rather than being owned by Abbott as with the other Program Compounds. Accordingly, by way of example and without limiting the foregoing, Abbott's indemnification obligation under this Section 12.7 will arise upon (i) any impairment of Abbott's ability to perform its obligations under this Agreement in the entire Territory as a result of Abbott's rights to the Program Compounds known as ABT-773, ABT-442 and ABT-751 arising from the Taisho Agreement, Wakunaga Agreement and the Eisai Agreement, respectively or (ii) a breach by Abbott or any other person of any of the In-License Agreements; except, in each case, to the extent any such Losses are the result of (A) any breach by John Hancock of its representations, warranties or obligations hereunder, or (B) any negligence, recklessness, or intentional misconduct by John Hancock or its Affiliates, agents, directors, employees.

12.8 Procedure. If John Hancock or any of its Affiliates, agents, directors or employees (each, an "Indemnitee") intends to claim indemnification under this Article 12, it shall

-30-

promptly notify Abbott (the "Indemnitor") of any Loss or action in respect of which the Indemnitor intends to claim such indemnification, and the Indemnitor shall have the right to participate in, and, to the extent the Indemnitor so desires, to assume the defense thereof with counsel selected by the Indemnitor; provided, however, that an Indemnitor shall have the right to retain its own counsel, with the fees and expenses of such counsel to be paid by the Indemnitor, if representation of such Indemnitor by the counsel retained by the Indemnitor would be inappropriate due to actual or potential differing interests between such Indemnitor and any other party represented by such counsel in such proceedings. The indemnity obligation in this Article 12 shall not apply to amounts paid in settlement of any loss, claim, damage, liability or action if such settlement is effected without the consent of the Indemnitor, which consent shall not be withheld unreasonably or delayed. The failure to deliver notice to the Indemnitor within a reasonable time after the commencement of any such action, if materially prejudicial to its ability to defend such action, shall relieve the Indemnitor of any liability to the Indemnitor under this Article 12 only to the extent arising from the tardiness or absence of such notice, but the omission so to deliver notice to the Indemnitor will not relieve it of any liability that it may have to any Indemnitor otherwise than under this Article 12. The Indemnitor shall cooperate fully with the Indemnitor and its legal representatives in the investigation of any action, claim or liability covered by indemnification under this Article 12, at the expense of the Indemnitor.

12.9 Insurance. Abbott shall at its expense maintain, through self-insurance or otherwise, product liability insurance with respect to the development, manufacture, sale and use of Products and Program Compounds in such amounts and on such terms as Abbott customarily maintains with respect to its other similar products. Abbott shall maintain such insurance for so long as it continues to develop, manufacture or sell any Products or Program Compounds, and thereafter for so long as Abbott customarily currently maintains such insurance.

12.10 Acknowledgment. Abbott and John Hancock acknowledge that Abbott has not delivered or disclosed the contents of any of the In-License Agreements to John Hancock.

ARTICLE 13 FORCE MAJEURE

Neither party shall be held liable or responsible to the other party nor be deemed to have defaulted under or breached this Agreement for failure or delay in fulfilling or performing any term of this Agreement when such failure or delay is caused by or results from causes beyond the reasonable control of the affected party including but not limited to fire, floods, embargoes, war, acts of war (whether war be declared or not), insurrections, riots, civil commotions, strikes, lockouts or other labor disturbances, acts of God or acts, omission or delays in acting by any governmental authority; provided that such affected party shall provide the other party with prompt notice of the circumstances surrounding such a material failure or delay, after which the parties will amend this Agreement upon terms and conditions that are mutually agreeable to equitably account to the party that does not so fail or delay.

CONFIDENTIAL
JH 008110

-31-

ARTICLE 14
ASSIGNMENT

Except as expressly provided hereunder, this Agreement may not be assigned or otherwise transferred, nor may any right or obligations hereunder be assigned or transferred by either party without the consent of the other party; and, in addition, both parties acknowledge and agree that the obligations of Abbott hereunder are personal to Abbott and that Abbott is uniquely qualified to perform them; provided, however, that either party shall be obligated to assign this Agreement and its rights and obligations hereunder in connection with the transfer or sale of all or substantially all of its business, or in the event of its merger or consolidation or change in control or similar transaction and in such event such party shall cause its successor or transferee in such transaction to assume all of the obligations of such party. Any permitted assignee shall assume all obligations of its assignor under this Agreement. Notwithstanding the foregoing, John Hancock shall have the right to assign its rights (but not its obligation to make payments under Section 3.1) in whole or in part (provided that, any assignment in part shall mean an assignment of a pro rata share of the entirety of John Hancock's rights hereunder) without Abbott's consent (and following any such assignment all references to John Hancock herein shall include any such assignee), provided that: (i) each assignee of such rights must be a bank, insurance company or other institutional investor; (ii) there shall be no greater than five (5) assignees; (iii) if any such assignee is located outside the United States John Hancock shall notify Abbott at least sixty (60) days in advance; (iv) if any claim arises with respect to Abbott's failure to make payments, then during the term of the Research Program (but in any event not longer than four years from the date hereof), any such claim must be brought by John Hancock, and not an assignee. In soliciting potential assignees for such right to payments, John Hancock shall not disclose any Confidential Information hereunder to more than ten (10) potential assignees. Any potential assignee to whom John Hancock discloses Confidential Information must have executed a confidentiality agreement no less stringent than Article 10 hereof. Furthermore, if John Hancock plans to exercise its right of assignment hereunder, John Hancock shall first notify Abbott of such plans in writing. Abbott shall have the first right to negotiate the purchase of any such assignment rights. If within fifteen (15) days after receipt of such notice the parties have not agreed upon the principal terms of such arrangement or if within forty-five (45) days after receipt of such notice the parties have not executed a final written agreement reflecting such arrangement, then John Hancock shall have no further obligations to Abbott with respect to such first right of negotiation.

ARTICLE 15
SEVERABILITY

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Each party hereby agrees that it does not intend its execution and delivery hereof or its performance hereunder to violate any public policy, statutory or common laws, rules, regulations, treaty or decision of any government agency or executive body thereof of any country or community or association of countries. If and to the extent any term or provision of this Agreement is held to be invalid, illegal or unenforceable by a court or other governmental

-32-

authority of competent jurisdiction, such invalidity, illegality or unenforceability shall not affect any other term or provision of this Agreement, which shall remain in full force and effect. The holding of a term or provision to be invalid, illegal or unenforceable in a jurisdiction shall not have any effect on the application of the term or provision in any other jurisdiction.

ARTICLE 16
MISCELLANEOUS

16.1 Notices. Any consent, notice or report required or permitted to be given or made under this Agreement by one of the parties hereto to the other shall be in writing, delivered personally or by facsimile (and promptly confirmed by personal delivery, U.S. first class mail or courier), U.S. first class mail or courier, postage prepared (where applicable), addressed to such other party at its address indicated below, or to such other address as the addressee shall have last furnished in writing to the addressor and (except as otherwise provided in this Agreement) shall be effective upon receipt by the addressee.

If to John Hancock: John Hancock Life Insurance Company
200 Clarendon Street, T-57
Boston, MA 02117
Attention: Bond & Corporate Finance Group
Telephone: 617-572-9624
Fax: 617-572-1628

copy to: John Hancock Life Insurance Company
200 Clarendon Street, T-50
Boston, MA 02117
Attention: Investment Law Division
Telephone: 617-572-9205
Fax: 617-572-9268

and, if it relates to making or not making a royalty payment or Milestone Payment hereunder,

copy to: John Hancock Life Insurance Company
200 Clarendon Street
Boston, MA 02117
Attention: Manager, Investment Accounting Division, B-3
Fax: 617-572-0628

CONFIDENTIAL
JH 008112

-33-

If to Abbott: Abbott Laboratories
Dept. 309, Bldg. AP30
200 Abbott Park Road
Abbott Park, IL 60064-3537
Attention: President, Pharmaceutical Products Division
Telephone: 847-938-6863
Fax: 847-938-5383

copy to: General Counsel
Abbott Laboratories
Dept. 364, Bldg. AP6D
100 Abbott Park Road
Abbott Park, IL 60064-6020
Telephone: 847-937-8905
Fax: 847-938-6277

16.2 Applicable Law. The Agreement shall be governed by and construed in accordance with the internal laws of the State of Illinois. With respect to any action hereunder, Abbott, to the extent that it may lawfully do so, hereby consents to service of process, and to be sued, in the Commonwealth of Massachusetts and consents to the exclusive jurisdiction of the courts of the Commonwealth of Massachusetts and the United States District Court for the District of Massachusetts, as well as to the jurisdiction of all courts to which an appeal may be taken from such courts, for the purpose of any suit, action or other proceeding arising out of any of its obligations hereunder or thereunder or with respect to the transactions contemplated hereby or thereby, and expressly waives any and all objections it may have as to venue in any such courts. Abbott further agrees that a summons and complaint commencing an action or proceeding in any of such courts shall be properly served and shall confer personal jurisdiction if served personally or by certified mail to it at its address for notices as provided in this Agreement or as otherwise provided under the laws of the Commonwealth of Massachusetts. THE PARTIES EACH IRREVOCABLY WAIVE ALL RIGHT TO A TRIAL BY JURY IN ANY SUIT, ACTION OR OTHER PROCEEDING INSTITUTED BY OR AGAINST IT IN RESPECT OF ITS OBLIGATIONS HEREUNDER OR THEREUNDER OR THE TRANSACTIONS CONTEMPLATED HEREBY OR THEREBY.

16.3 Entire Agreement This Agreement contains the entire understanding of the parties with respect to the subject matter hereof. All express or implied agreements and understandings, either oral or written, with respect to the subject matter hereof heretofore made are expressly merged in and made a part of this Agreement. This Agreement may be amended, or any term hereof modified, only by a written instrument duly executed by both parties hereto.

16.4 Headings. The captions to the several Articles and Sections hereof are not a part of this Agreement, but are merely guides or labels to assist in locating and reading the several Articles and Sections hereof.

CONFIDENTIAL
JH 008113

-34-

16.5 Independent Contractors. It is expressly agreed that John Hancock and Abbott shall be independent contractors and that the relationship between the two parties shall not constitute a partnership, joint venture or agency. Neither John Hancock nor Abbott shall have the authority to make any statements, representations or commitments of any kind, or to take any action, which shall be binding on the other, without the prior written consent of the other party to do so.

16.6 Performance By Affiliates, Licensees and Subcontractors. The parties recognize that Abbott may carry out certain obligations under this Agreement through performance by its Affiliates, Licensees and Subcontractors (but in no event shall that relieve Abbott of any of its obligations hereunder). Abbott guarantees that the activities of its Affiliates, Licensees and Subcontractors under this Agreement shall comply with this Agreement.

16.7 Dispute Resolution. The parties shall attempt to amicably resolve disputes arising between them regarding the validity, construction, enforceability or performance of the terms of this Agreement, and any differences or disputes in the interpretation of the rights, obligations, liabilities and/or remedies hereunder, which have been identified in a written notice from one party to the other, by good faith settlement discussions between the President of Abbott's Pharmaceutical Products Division and a Managing Director of John Hancock or his designee. The parties agree that, prior to filing any lawsuit regarding any dispute that arises in connection with this Agreement (with the exception of any action demanding a preliminary injunction), such representatives shall meet and attempt to amicably resolve such dispute within thirty (30) days after the receipt of such written notice.

16.8 Waiver. The waiver by either party hereto of any right hereunder or the failure to perform or of a breach by the other party shall not be deemed a waiver of any other right hereunder or of any other breach or failure by said other party whether of a similar nature or otherwise.

16.9 Counterparts. This Agreement may be executed in two or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

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CONFIDENTIAL
JH 008114

-35-

IN WITNESS WHEREOF, the parties have executed this Agreement as of the date first set forth above.

JOHN HANCOCK LIFE
INSURANCE COMPANY

ABBOTT LABORATORIES

By: Stephen J. Blewitt
Name: Stephen J. Blewitt
Title: Managing Director
Date: March 13, 2001

By: Jeffrey M. Leiden
Name: Jeffrey M. Leiden, Ph.D., M.D.
Title: Executive Vice President, Pharmaceuticals
and Chief Scientific Officer
Date: March 13, 2001

JOHN HANCOCK VARIABLE
LIFE INSURANCE COMPANY

By: Stephen J. Blewitt
Name: Stephen J. Blewitt
Title: Authorized Signatory
Date: March 13, 2001

INVESTORS PARTNER LIFE INSURANCE
COMPANY

By: Stephen J. Blewitt
Name: Stephen J. Blewitt
Title: Authorized Signatory
Date: March 13, 2001

CONFIDENTIAL
JH 008115

-36-

EXHIBIT 1.6

FIRST ANNUAL RESEARCH PLAN

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JH 008116

Ketolide Oral & IV (ABT-773)
Annual Development Plan
Exhibit 1.6

Therapeutic Area	Antibacterial																													
Indications	Adult Tablet: Community-acquired respiratory infections. I.V.: Step-down therapy in community-acquired hospitalized pneumonia.																													
Description	<ul style="list-style-type: none">• ABT-773 is a potent ketolide with strong activity against most macrolide resistant strains, while maintaining the broad spectrum coverage of clarithromycin.• Product will be available as tablet and IV formulation.• ABT-773 will address the major unmet medical needs of increasing resistance to current empiric agents, particularly <i>S. pneumoniae</i>.• Maintains clarit's claim of "Spans the spectrum" (G+, G-, atypicals).• Cover key G+ resistant strains (<i>S. pneumoniae</i>, <i>S. pyogenes</i>).• Tablet dosing is 150mg QD or 150mg BID dosing based on severity of indications.• Tablet: 5 days for ABSCB, pharyngitis, 10 days for AMS and CAP.• Incidence of GI side effects equal to clarit (assuming comparable drug levels to tablet).• COGS target \$2,500/kg at launch for tablet.																													
Current Time Line	<table><tr><th>Milestones</th><th>Tablet Date</th><th>IV Date</th></tr><tr><td>Phase I</td><td>1Q1997</td><td>1Q2001</td></tr><tr><td>Phase IIb</td><td>3Q1998</td><td>N/A</td></tr><tr><td>Phase III</td><td>4Q2000</td><td>4Q2001</td></tr><tr><td>NDA Filing</td><td>3Q2002</td><td>2Q2003</td></tr><tr><td>Launch</td><td>1Q2004</td><td>2Q2004</td></tr></table>	Milestones	Tablet Date	IV Date	Phase I	1Q1997	1Q2001	Phase IIb	3Q1998	N/A	Phase III	4Q2000	4Q2001	NDA Filing	3Q2002	2Q2003	Launch	1Q2004	2Q2004					<table><tr><th>Spending</th><th>\$</th></tr><tr><td>Project-to-Date-Spending (thru '00)</td><td>188.4</td></tr><tr><td>2001 Current Projection (Plan)</td><td>91.5*</td></tr></table> <p>* See page 2 for detail.</p>	Spending	\$	Project-to-Date-Spending (thru '00)	188.4	2001 Current Projection (Plan)	91.5*
Milestones	Tablet Date	IV Date																												
Phase I	1Q1997	1Q2001																												
Phase IIb	3Q1998	N/A																												
Phase III	4Q2000	4Q2001																												
NDA Filing	3Q2002	2Q2003																												
Launch	1Q2004	2Q2004																												
Spending	\$																													
Project-to-Date-Spending (thru '00)	188.4																													
2001 Current Projection (Plan)	91.5*																													
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total																							
	74.1	91.5	89.0	45.0	32.0	22.0	333.6																							

CONFIDENTIAL
JH 008117

Ketolide (ABT-773)
2001 Plan Development Cost Summary

Program Status		1999				2000				2001				2002				2003				2004			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Phase IIb (Tablet)																									
Phase III (Tablet)																									
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Endothelin (ABT-627)
Annual Development Plan
Exhibit 1.6

Therapeutic Area	Oncology						
Indications	<ul style="list-style-type: none">- Hormone Refractory Prostate Cancer- Potential for use in early Prostate Cancer and other cancer types						
Description	<ul style="list-style-type: none">- ABT-627 is Abbott's leading endothelin antagonist receptor- ABT-627 is seeking an indication for the treatment of hormone refractory prostate cancer- ABT-627 will probably be used with current therapies- Well tolerated as chronic therapy- Oral administration- No major drug interactions with drugs commonly used in elderly population or hormonal therapy- Demonstrated cost effectiveness at filing						
Current Time Line	Milestone	Date				Spending	\$5
	Phase I	2Q1996				Project-to-Date Spending (thru '00)	127.6
	Phase II	4Q1997					
	Phase III	4Q2000					
	NDA Filing	2Q2004				2001 Current Projection (Plan)	38.0*
	Launch	4Q2004					
* See page 2 for detail.							
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total
PC*	13.0	35.0	40.0	33.0	20.0	10.0	164.0
EPcA*	N/A	6.0	6.0	5.0	0.0	0.0	17.0
FE*	N/A	5.0	3.0	0.0	0.0	0.0	8.0
* End of Phase II meeting with FDA just completed. Budget Impact still in process plus discussion of other cancer indications ongoing. 2001 range \$35-40 depending on outcome of discussion.							

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2001 Plan Development Cost Summary

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CCM (ABT-594)
Annual Development Plan
Exhibit 1.6

Therapeutic Area	Neuroscience																										
Indications	ABT-594 primary target indication is the treatment of neuropathic pain (NP).																										
Description	<ul style="list-style-type: none">- ABT-594 is a non-opioid, non-NSAID analgesic that is a potent and selective neuronal nicotinic receptor modulator.- ABT-594 is effective in nociceptive pain and neuropathic pain.- ABT-594 is expected to have a better side effect profile than opioids, no tolerance, no abuse, and no DEA scheduling.- Pre clinical data show ABT-594 to be 30 to 100 times more potent and equally efficacious to morphine in treating moderate to severe pain in several well characterized animal models of pain.- ABT-594 has a unique mechanism of action which may enable use in combination with other analgesics as well as monotherapy.- Slow onset of action (approx. 1.5 - 3 hours) at low doses tested may suggest limited utility in acute pain types.- Favorable safety profile.- Oral formulation, BID dosing.																										
Current Time Line	<table><tr><th>Milestones</th><th>Date</th></tr><tr><td>IND Filing</td><td>4Q1996</td></tr><tr><td>Phase I</td><td>3Q1997</td></tr><tr><td>Phase II</td><td>3Q1998</td></tr><tr><td>Phase III</td><td>4Q2001</td></tr><tr><td>NDA Filing</td><td>3Q2003</td></tr><tr><td>Launch</td><td>3Q2004</td></tr></table>	Milestones	Date	IND Filing	4Q1996	Phase I	3Q1997	Phase II	3Q1998	Phase III	4Q2001	NDA Filing	3Q2003	Launch	3Q2004	<table><tr><th>Spending</th><th>\$\$</th></tr><tr><td>Project-to-Date-Spending (thru '00)</td><td>97.3</td></tr><tr><td>2001 Current Projection (Plan)</td><td>35.0*</td></tr></table>				Spending	\$\$	Project-to-Date-Spending (thru '00)	97.3	2001 Current Projection (Plan)	35.0*	* See page 2 for detail.	
Milestones	Date																										
IND Filing	4Q1996																										
Phase I	3Q1997																										
Phase II	3Q1998																										
Phase III	4Q2001																										
NDA Filing	3Q2003																										
Launch	3Q2004																										
Spending	\$\$																										
Project-to-Date-Spending (thru '00)	97.3																										
2001 Current Projection (Plan)	35.0*																										
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total																				
	14.4	35.0	45.0	32.0	15.0	12.0	163.4																				

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ART-594

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JH 008122

Quinolone (ABT-492)
Annual Development Plan
Exhibit 1.6

Therapeutic Area	Anti-bacterial																								
Indications	- Community acquired respiratory, nosocomial pneumonia, complicated and uncomplicated urinary tract and skin/soft tissue infections.																								
Description	<ul style="list-style-type: none">- ABT-492 is a potent broad-spectrum quinolone with activity against Gram+, Gram-, and atypical pathogens, including most penicillin, macrolide, and quinolone resistant strains of <i>S. pneumoniae</i>.- Commercial objective is "Trovan-like" activity with "Levaquin-like" safety.- Preliminary in-vitro safety assays suggest good safety profile.- Product will be available in tablet and injectable formulations.- Targeting QD dosing for both formulations (not confirmed).- Targeting 5-7 day dosing for most indications (not confirmed).- COGS at \$1,500-3,200/kg at launch pending chemistry optimization.																								
Current Time Line	<table><tr><th>Milestone</th><th>Date</th></tr><tr><td>Phase I</td><td>4Q2000</td></tr><tr><td>Phase II</td><td>3Q2001</td></tr><tr><td>Phase III</td><td>3Q2002</td></tr><tr><td>NDA Filing</td><td>4Q2004</td></tr><tr><td>Launch</td><td>4Q2005</td></tr></table>	Milestone	Date	Phase I	4Q2000	Phase II	3Q2001	Phase III	3Q2002	NDA Filing	4Q2004	Launch	4Q2005	<table><tr><th>Spending</th><th>\$M</th></tr><tr><td>Project-to-Date-Spending (thru '00)</td><td>11.3</td></tr><tr><td>2001 Current Projection (Plan)</td><td>25.0*</td></tr></table>				Spending	\$M	Project-to-Date-Spending (thru '00)	11.3	2001 Current Projection (Plan)	25.0*	* See page 2 for detail.	
Milestone	Date																								
Phase I	4Q2000																								
Phase II	3Q2001																								
Phase III	3Q2002																								
NDA Filing	4Q2004																								
Launch	4Q2005																								
Spending	\$M																								
Project-to-Date-Spending (thru '00)	11.3																								
2001 Current Projection (Plan)	25.0*																								
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total																		
	5.5	25.0	75.0	100.0	52.0	11.0	269.5																		

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Program Status

	2000				2001				2002				2003				2004				2005			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Phase I																								
Phase II																								
Phase III																								

NOA Launch

Major Development Activities and Costs

Clinical Program	Total Patients	Enrolled 8/31/2000	Start	End	2000 AGU Cost	2001 Plan Cost
Phase I						
Single Rising Dose / Food Effects In Healthy Volunteers	116	0	Nov-00	Jan-01	\$500	\$170
Multiple Rising Dose In Healthy Volunteers	60	0	Nov-00	Apr-01	\$500	\$300
External PK Studies	N/A	0	Apr-01	Sep-01	\$0	\$900
Microbiology Studies	N/A	N/A	Jan-01	Dec-01	\$0	\$713
Phase IIA - AECB	250	0	Aug-01	Apr-02	\$0	\$2,083
Phase IIB - CAP	250	0	Nov-01	Jul-02	\$0	\$833
Venture Management					\$201	\$1,320
European Venture Research					\$28	\$58
Phase I Center					\$70	\$130
Data Management/Statistics					\$53	\$489
					\$1,352	\$6,869

Chemistry, Manufacturing, and Controls (CMC)

Bulk Drug / Process Formulation & Analytical	2000 AGU	2001 Plan
	\$598	\$7,872
	\$593	\$961
	\$1,191	\$8,833

Drug Safety Support Ongoing Drug Safety support including: Toxicity Studies

	2000 AGU	2001 Plan
	\$1,841	\$2,331
	\$1,941	\$2,331

Other Support Costs

	2000 AGU	2001 Plan
Discovery	\$2,208	\$3,224
Reg. / Res. Quality Assurance / Investigational Drug QA	\$110	\$534
Medical Affairs	\$0	\$35
Other	\$0	\$47
Milestone Payments (Initiation of Phase IIA)	\$0	\$3,000
	\$2,318	\$6,840

Total Program

	2000 AGU	2001 Plan
	\$5,800	\$25,000

TSP (ABT-510)
Annual Development Plan
Exhibit 1.6

Therapeutic Area	Oncology												
Indications	Solid tumors such as lung, breast, ovary, bladder and pancreas.												
Description	<ul style="list-style-type: none">- Thrombospondin peptide- Novel anti-angiogenesis agent- Parenteral dosing- ABT-510 is seeking an indication for the treatment of solid tumors- Mechanism may prevent the growth of tumors and prevent the spread of metastases by preventing or inhibiting the growth of nutrient supplying blood vessels												
Current Time Line	Milestone	Date					<table><tr><td>Spending</td><td>\$5</td></tr><tr><td>Project-to-Data-Spending (thru '00)</td><td>45.6</td></tr><tr><td>2001 Current Projection (Plan)</td><td>9.0*</td></tr></table> <p>* See page 2 for detail.</p>	Spending	\$5	Project-to-Data-Spending (thru '00)	45.6	2001 Current Projection (Plan)	9.0*
Spending	\$5												
Project-to-Data-Spending (thru '00)	45.6												
2001 Current Projection (Plan)	9.0*												
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total						
	6.6	9.0	37.0	29.0	23.0	15.0	119.6						

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2001 Plan Development Cost Summary

[illegible]

JH 008126

MMPI (ABT-518)
Annual Development Plan
Exhibit 1.6

Therapeutic Area	Oncology						
Indications	Solid tumors such as lung, ovarian, pancreas, breast, colorectal and bladder.						
Description	<ul style="list-style-type: none"> - Novel metalloproteinase inhibitor. - Cytostatic mechanism. - Oral dosing. - May prevent the growth of metastatic lesions and/or inhibit primary tumor growth. - Superior efficacy or side-effect profile to competitive agents. 						
Current Time Line	Milestone	Date				Spending	\$
	DDC	1Q2000				Project-to-Date Spending (thru '00)	40.0
	Phase I	1Q2001				2001 Current Projection (Plan)	7.0*
	Phase II	3Q2002					
	Phase III	4Q2003					
	NDA Filing	4Q2005					
	Launch	2Q2006					
	* See page 2 for detail.						
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total
	5.0	7.0	31.0	35.0	26.0	20.0	124.0

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2001 Plan Development Cost Summary

Program Status	1999				2000				2001				2002				2003				2004				2005				2006			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4				
Phase I																																
Phase II																																
Phase III																																
NDA																																

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Anti-Mitotic (ABT-751)
Annual Development Plan
Exhibit 1.6

Therapeutic Area	Oncology							
Indications	Solid tumors such as breast, lung, colorectal, and ovarian							
Description	<ul style="list-style-type: none">• Novel oral cytotoxic agent that inhibits tumor growth by inhibiting the polymerization of tubulin, similar to the MOA of taxanes• May be effective in patients resistant to other cytotoxic agents							
Current Time Line	Milestone	Date					Spending	\$5
	In-Licensure	2Q/2000					Project-to-Date-Spending (thru '00)	6.0
	Phase I	1Q/2001						
	Phase II	4Q/2001						
	Phase III	4Q/2002					2001 Current Projection (PLAN)	10.0*
	NDA Filing	1Q/2005						
	Launch	1Q/2005					* See page 2 for detail.	
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total	
	6.0	10.0	27.0	35.0	25.0	12.0	115.0	

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2001 Plan Development Cost Summary

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FTI (ABT-xxx)
Annual Development Plan
Exhibit 1.6

Therapeutic Area	Oncology																									
Indications	Solid tumors such as lung, breast, ovary, bladder and pancreas.																									
Description	<ul style="list-style-type: none">- Farnesyltransferase inhibitor.- Mechanism of action is Unknown, but thought to inhibit farnesylated proteins which are integral for malignant tumor growth.																									
Current Time Line	<table><tr><th>Milestones</th><th>Date</th></tr><tr><td>DDC</td><td>1Q/2001</td></tr><tr><td>Phase I</td><td>4Q/2001</td></tr><tr><td>Phase II</td><td>2Q/2003</td></tr><tr><td>Phase III</td><td>3Q/2004</td></tr><tr><td>NDA Filing</td><td>4Q/2006</td></tr><tr><td>Launch</td><td>4Q/2007</td></tr></table>	Milestones	Date	DDC	1Q/2001	Phase I	4Q/2001	Phase II	2Q/2003	Phase III	3Q/2004	NDA Filing	4Q/2006	Launch	4Q/2007	<table><tr><th>Spending</th><th>\$M</th></tr><tr><td>Project-to-Date-Spending (thru '00)</td><td>36.0</td></tr><tr><td>2001 Current Projection (Plan)</td><td>6.0*</td></tr></table> <p>* See page 2 for details.</p>					Spending	\$M	Project-to-Date-Spending (thru '00)	36.0	2001 Current Projection (Plan)	6.0*
Milestones	Date																									
DDC	1Q/2001																									
Phase I	4Q/2001																									
Phase II	2Q/2003																									
Phase III	3Q/2004																									
NDA Filing	4Q/2006																									
Launch	4Q/2007																									
Spending	\$M																									
Project-to-Date-Spending (thru '00)	36.0																									
2001 Current Projection (Plan)	6.0*																									
Projected Spending by Year	<table><tr><th>2000</th><th>2001</th><th>2002</th><th>2003</th><th>2004</th><th>2005</th><th>Total</th></tr><tr><td>N/A</td><td>6.0</td><td>15.0</td><td>30.0</td><td>30.0</td><td>18.0</td><td>99.0</td></tr></table>	2000	2001	2002	2003	2004	2005	Total	N/A	6.0	15.0	30.0	30.0	18.0	99.0											
2000	2001	2002	2003	2004	2005	Total																				
N/A	6.0	15.0	30.0	30.0	18.0	99.0																				

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ONCOLOGY - FTI ABT-xxx
2001 Plan Development Cost Summary

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Dopamine Receptor Agonist (ABT-xxx)
Annual Development Plan
Exhibit 1.6

Therapeutic Area	Other						
Indications	Male Erectile Dysfunction (MED)						
Description	<ul style="list-style-type: none"> • D4 Dopamine Receptor Agonist. • Targets D4 receptors in the brain which offers the potential for efficacy in patients with MED that do not respond to Viagra. • Additionally this approach offers opportunity for compounds with improved tolerability relative to other Dopamine agents that are clinically used for MED. 						
Current Time Line	Milestones	Date					Spending
	DDC	4Q/2001					\$5
	Phase I	2Q/2002					Project-to-Date Spending (thru '00)
	Phase II	4Q/2003					35.0
	Phase III	1Q/2005					2001 Current Projection (Plan)
	NOA Filing	1Q/2007					6.0*
	Launch	4Q/2007					* See page 2 for detail.
Projected Spending by Year	2000	2001	2002	2003	2004	2005	Total
	N/A	6.0	15.0	30.0	30.0	18.0	99.0

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Dopamine Receptor Agonist ABT-xxx
2001 Plan Development Cost Summary

Program Status	2000				2001				2002				2003				2004				2005				2006				2007			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4				
Phase I																																
Phase II																																
Phase III																																

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Pharmaceutical Products Division
Sample Direct/Indirect Project Funding Distribution
2001 Plan (\$000)

	ADT - 775 (Late Stage - Phase III)			MMPI (Early Stage)		
	Direct	Indirect	Total	Direct	Indirect	Total
PPD Investigational Drug	0.3	0.0	0.4	-	-	-
Venture Management	4.8	1.6	6.5	0.8	0.2	0.9
Discovery	2.2	0.2	2.4	1.1	0.3	1.3
Drug Safety	1.6	0.2	1.7	1.8	0.3	2.1
PARD	4.8	0.4	5.3	0.8	0.2	1.0
Phase I Center	2.0	0.1	2.1	0.1	0.0	0.1
Development Operations	4.2	0.5	4.6	0.1	0.0	0.1
Regulatory Affairs	0.2	0.0	0.3	0.0	0.0	0.0
Medical Affairs	0.8	0.1	0.9	0.0	0.0	0.0
Administration	1.6	-	1.6	0.1	-	0.1
AI Manpower	0.7	-	0.7	-	-	-
Bulk Drug / Process	15.0	-	15.0	-	-	-
Clinical Grants	43.1	-	43.1	1.3	-	1.3
Total	<u>81.4</u>	<u>1.2</u>	<u>84.6</u>	<u>6.2</u>	<u>0.9</u>	<u>7.1</u>
% Split	96.2%	3.8%	100.0%	86.6%	13.4%	100.0%

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Pharmaceutical Products Division
Sample Direct/Indirect Rate & Headcount Distribution
2001 Plan

<u>Rate:</u>	<u>Data Management</u>	<u>Toxicology/Pathology</u>
Direct		
Payroll (Both PMP and Supv/Mgr)	6,577	5,277
Office Supplies	53	51
T & E	26	84
Sem/Edu	21	73
Supplies	41	440
Consultant	291	67
Printing	73	4
Clinical Tracking Costs	4,075	---
Depreciation	1,031	258
UNIX Based Support	3,453	921
Utilities	62	---
Floorspace	579	1,479
Housekeeping	23	---
Other	112	389
Sub-Total Direct	16,416	9,042
Indirect		
Patents & Trademarks	285	388
Corporate Indirect	697	949
PPD Indirect (Mgmt.)	337	458
Department Overhead	396	584
Other	46	62
Sub-Total Indirect	1,761	2,441
Total	18,177	11,483
% Direct	90%	79%
% Indirect	10%	21%
 <u>Headcount:</u>		
Direct Headcount	123 88%	53 88%
Indirect Headcount	17 12%	7 12%
Total Headcount	140	60
 Rate	92.06	135.42
Hours	1,600	1,600
Annual Rate	147,296	216,672

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-37-

EXHIBIT 1.17

EISAI TERRITORY

1. Bhutan
2. Brunei
3. Cambodia
4. People's Republic of China
5. Republic of China (Taiwan)
6. India
7. Indonesia
8. Japan
9. Democratic People's Republic of Korea (North Korea)
10. Republic of Korea
11. Laos
12. Macao
13. Malaysia
14. Mongolia
15. Myanmar
16. Nepal
17. Pakistan
18. Papua New Guinea
19. Philippines
20. Singapore
21. Sri Lanka
22. Thailand
23. Vietnam
24. Italy, co-exclusive rights with Abbott, unless Abbott exercises its rights under the terms of the Eisai Agreement to take an exclusive right to Italy.

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-38-

EXHIBIT 1.40

PROGRAM COMPOUNDS

<u>In-License Agreement</u>	<u>Program Compound</u>	<u>Development Phase</u>
Taisho	ABT-627 (Endothelin antagonist)	phase III
	ABT-773 (Ketolide antibiotic)	phase III
	ABT-594 (Cholinergic channel modulator)	late phase II
Wakunaga	ABT-492 (Quinolone antibiotic)	phase I
Eisai	ABT-751 (Antimitotic)	phase I
	ABT-510 (Thrombospondin peptide)	phase I
<u>Preclinical Programs:</u>		
FTI Program		late preclinical
ED Program		late preclinical
MMPI Program	ABT-518 (Matrix metalloproteinase inhibitor)	phase I

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-39-

EXHIBIT 1.43

EXAMPLE OF PROGRAM RELATED COSTS FOR ONE PROGRAM COMPOUND

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2001 KEY RATES									
	2000			2001			% Change		
	Rate	Hours	Annual Rate	Rate	Hours	Annual Rate	Hourly Rate	Total Hours	Annual Rate
<u>DRUG SAFETY</u>									
Toxicology/Pathology - PMP/TMP	121.52	1,680	204,154	135.42	1,600	216,672	11.4%	-4.8%	6.1%
Metabolism/Microscopy - PMP/TMP	144.75	1,600	231,600	141.64	1,650	233,706	-2.1%	3.1%	0.9%
Comparative Medicine - PMP/TMP	115.60	1,768	204,381	116.88	1,850	216,228	1.1%	4.6%	5.8%
Strategic & Exploratory - PMP/TMP	121.52	1,680	204,154	173.56	1,600	277,696	42.8%	-4.8%	36.0%
<u>PHASE I CENTER</u>									
Pharmacokinetics 4PK - PMP/TMP	144.75	1,600	231,600	135.00	1,600	216,000	-6.7%	...	-6.7%
Clin. Res. MDs 42P - PMP	180.35	1,500	270,525
Clin Res. Spec. 420-PMP/TMP	113.59	1,700	193,103	123.75	1,700	210,375	8.9%	...	8.9%
<u>PARD</u>									
Prod Dev - PMP, TMP	108.54	1,800	195,372	116.71	1,800	210,078	7.5%	...	7.5%
IDS - PMP, TMP	160.80	1,600	257,280	162.11	1,600	259,376	0.8%	...	0.8%
<u>DEV OPERATIONS</u>									
Data Mgmt D433 - TMP/PMP	90.04	1,600	144,064	92.08	1,600	147,296	2.2%	...	2.2%
Stats - PMP/TMP	97.75	1,800	175,950	99.10	1,800	178,380	1.4%	...	1.4%
<u>RA/QA</u>									
RA/QA - PMP & TMP	125.50	1,600	200,800	134.49	1,600	215,184	7.2%	...	7.2%
<u>DISCOVERY</u>									
	137.65	1,800	247,770	142.91	1,800	257,238	3.8%	...	3.8%

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JH 008140

-40-

EXHIBIT 9.2

PAYMENT INSTRUCTIONS

Fleet Boston
ABA No. 011000390
Boston, Massachusetts 02110
Account of: John Hancock Life Insurance Co. Private Placement Collection Acct.
Account Number: 541-55417
On Order of: Abbott Laboratories -- Research Funding Agreement dated as of March 13, 2001

E-3233160

CONFIDENTIAL
JH 008141

-41-

Exhibit 12.2(d)

Further Information Regarding Program Compounds

COMPOUND	CHEMICAL NAME	CURRENT STAGE OF DEVELOPMENT
ABT-627 Endothelin antagonist	(2R,3R,4S)-4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-(4-methoxyphenyl)-3-pyrrolidinecarboxylic acid	Phase III
ABT-773 Ketolide antibiotic	(3aS,4R,7R,9R,10R,11S,13R,15R,15aR)-4-ethyl-3a,7,9,11,13,15-hexamethyl-2,6,8,14-tetraoxo-11-[[2(E)-3-(3-quinoliny)-2-propenyl]oxy]tetradecahydro-2H-oxacyclotetradecino[4,3-d][1,3]oxazol-10-yl 3,4,6-trideoxy-3-(dimethylamino)--D-xyllo-hexopyranoside	Phase III
ABT-594 Cholinergic channel modulator	(2R)-azetidinylmethyl 6-chloro-3-pyridinyl ether hydrochloride	Phase II
ABT-492 Quinoline Antibiotic	potassium 1-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-7-(3-hydroxy-1-azetidinyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate	Phase I
ABT-518 Matrix metalloproteinase inhibitor	(1S)-1-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-[(4-{4-(trifluoromethoxy)phenoxy}phenyl)sulfonyl]ethyl(hydroxy)formamide	Phase I
ABT-751 Antimitotic	N-[2-(4-hydroxyanilino)-3-pyridinyl]-4-methoxybenzenesulfonamide	Phase I
Farnesyltransferase inhibitor	N.A.	Pre-Clinical Program
Dopamine Receptor Agonist for Erectile Dysfunction	N.A.	Pre-Clinical Program

CONFIDENTIAL
JH 008142

-42-

EXHIBIT 12.2(e)

Certain Patent Information

ABT-627

COUNTRY	FILING DATE	PATENT NUMBER	STATUS	EXP. DATE
Australia	08/04/1995	711832	Issued	08/04/2015
Brazil	02/12/1997		Pending	
Canada	08/04/1995		Pending	
EP*	08/04/1995		Pending	
Hong Kong	07/15/1998		Pending	
Israel	08/10/1995		Pending	
Japan	08/04/1995		Pending	
Korea	08/04/1995		Pending	
Mexico	08/04/1995		Pending	
Philippines	08/17/1995		Pending	
USA	05/30/1995	5,767,144	Issued	06/16/2015

*Europe: Austria, Belgium, Great Britain, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, Switzerland

CONFIDENTIAL
JH 008143

-43-

Exhibit 12.2(e) (Cont'd)

ABT-773

(Subject to Taisho Agreement)

COUNTRY	FILING DATE	PATENT NUMBER	STATUS	EXP. DATE
Argentina	09/03/1997		Pending	
Australia	09/02/1997		Pending	
Brazil	05/13/1997		Pending	
Brazil	09/02/1997		Pending	
Bulgaria	09/02/1997		Pending	
Belarus	09/02/1997		Pending	
China	09/02/1997		Pending	
Chile	09/04/1997		Pending	
Canada	09/02/1997		Pending	
Columbia	09/02/1997		Pending	
Czech Republic	09/02/1997		Pending	
EP*	09/02/1997		Pending	
Guatemala	08/29/1997		Pending	
Hong Kong	09/02/1997		Pending	
Croatia	09/03/1997		Pending	
Hungary	09/02/1997		Pending	
Indonesia	09/04/1997		Pending	
India	Pending-Black Box		Pending	
Israel	09/02/1997		Pending	
Japan	09/02/1997		Pending	
Korea	09/02/1997		Pending	
Mexico	09/02/1997		Pending	
Malaysia	08/26/1997		Pending	
Norway	09/02/1997		Pending	

CONFIDENTIAL
JH 008144

-44-

Exhibit 12.2(e) (cont'd)

ABT-773 (cont'd)
(Subject to Taisho Agreement)

COUNTRY	FILING DATE	PATENT NUMBER	STATUS	EXP. DATE
New Zealand	09/02/1997		Pending	
Philippines	09/02/1997		Pending	
Pakistan	10/13/1997	136010	Issued	10/13/2013
Poland	09/02/1997		Pending	
Romania	09/02/1997		Pending	
Russia	09/02/1997		Pending	
South Africa	08/20/1997	97/7474	Issued	08/20/2017
Singapore	09/02/1997		Pending	
Slovak Republic	09/02/1997		Pending	
Slovenia	09/02/1997	20023	Issued	09/02/2017
Saudi Arabia	02/10/1998		Pending	
Thailand	09/03/1997		Pending	
Turkey	09/02/1997	TR 01127 B	Issued	09/02/2017
Taiwan	09/05/1997		Pending	
UA	09/02/1997		Pending	
USA	07/03/1997	5,866,549	Issued	09/04/2016
Yugoslavia	09/02/1997		Pending	

*Europe: Austria, Belgium, Great Britain, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, Switzerland

CONFIDENTIAL
JH 008145

-45-

EXHIBIT 12.2(e) (Cont'd)

ABT-594

COUNTRY	FILING DATE	PATENT NUMBER	STATUS	EXP. DATE
Australia	10/08/1993	687017	Issued	10/18/2013
Brazil	04/30/1997		Pending	
Canada	10/08/1993		Pending	
EP*	10/08/1993		Pending	
Hong Kong	12/10/1998		Pending	
Israel	10/04/1993	107184	Issued	10/04/2013
Japan	10/08/1993	3098035	Issued	10/08/2013
Korea	10/08/1993		Pending	
Mexico	10/08/1993		Pending	
Philippines	10/07/1993		Pending	
USA	06/07/1995	5,948,793	Issued	09/07/2016

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CONFIDENTIAL
JH 008146

-46-

EXHIBIT 12.2(e) (Cont'd)

ABT-492

(Subject to Wakunaga Agreement)

COUNTRY	FILING DATE	PATENT NUMBER	STATUS	EXP. DATE
Australia	09/24/1999		Pending	
Brazil	11/29/1999		Pending	
Canada	12/06/1999		Pending	
China	10/22/1999	1258674A	Issued	
Hong Kong				
EP*	12/08/1999	0992501	Issued	
Hungary	11/23/1999	9904389	Issued	
Republic of Korea	08/29/2000			
Mexico	10/14/1999		Pending	
Russian Federation	05/26/2000		Pending	
USA	06/10/1999		Pending	
Japan	10/06/1999	2000-136191	Issued	

*Europe: Austria, Belgium, Switzerland, Germany, Denmark, Spain, Finland, France, Great Britain, Greece, Ireland, Italy, Luxembourg, Monaco, Netherlands, Portugal, Sweden

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JH 008147

-47-

EXHIBIT 12.2(e) (Cont'd)

ABT-510

COUNTRY	FILING DATE	PATENT NUMBER	STATUS	EXP. DATE
Argentina	05/21/1999		Pending	
Australia	05/21/1999		Filing in Process	
Brazil	05/21/1999		Filing in Process	
Bulgaria	05/21/1999		Filing in Process	
China	05/21/1999		Filing in Process	
Chile	05/20/1999		Pending	
Canada	05/21/1999		Filing in Process	
Columbia	05/21/1999		Pending	
Czech Republic	05/21/1999		Filing in Process	
EP*	05/21/1999		Filing in Process	
Hong Kong	05/21/1999		Filing in Process	
Hungary	05/21/1999		Pending	
India	05/21/1999		Filing in Process	
Israel	05/21/1999		Filing in Process	
Japan	05/21/1999		Filing in Process	
Korea	05/21/1999		Filing in Process	
Mexico	05/21/1999		Filing in Process	
Norway	05/21/1999		Filing in Process	
New Zealand	05/21/1999		Filing in Process	
Philippines	05/21/1999		Pending	
Poland	05/21/1999		Filing in Process	
South Africa	05/21/1999		Filing in Process	
Slovak Republic	05/21/1999		Filing in Process	
Saudi Arabia	05/21/1999		Pending	
Turkey	05/21/1999		Filing in Process	
Taiwan	05/21/1999		Pending	
USA	05/21/1999		Pending	

*Europe: Austria, Belgium, Great Britain, Cyprus, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Romania, Slovenia, Spain, Sweden, Switzerland

CONFIDENTIAL
JH 008148

-48-

EXHIBIT 12.2(e) (Cont'd)

ABT-518

COUNTRY	FILING DATE	PATENT NUMBER	STATUS	EXP. DATE
Argentina	07/30/1998		Pending	
Australia	07/27/1998		Pending	
Brazil	07/27/1998		Pending	
Bulgaria	07/27/1998		Pending	
China	07/27/1998		Pending	
Chile	07/17/1998		Pending	
Canada	07/27/1998		Pending	
Columbia	07/29/1998		Pending	
Czech Republic	07/27/1998		Pending	
EP*	07/27/1998		Pending	
Hungary	07/27/1998		Pending	
Israel	07/27/1998		Pending	
Japan	07/27/1998		Pending	
Korea	07/27/1998		Pending	
Mexico	07/27/1998		Pending	
Norway	07/27/1998		Pending	
New Zealand	07/27/1998		Pending	
Philippines	07/27/1998		Pending	
Poland	07/27/1998		Pending	
South Africa	07/30/1998	98/6628	Issued	07/30/2018
Slovak Republic	07/27/1998		Pending	
Saudi Arabia	12/15/1998		Pending	
Turkey	07/27/1998		Pending	
Taiwan	07/31/1998		Pending	
USA	08/05/1998		Pending	

*Europe: Austria, Belgium, Great Britain, Denmark, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, Switzerland

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JH 008149

-49-

EXHIBIT 12.2(c) (Cont'd)

ABT-751
(Subject to Eisai Agreement)

COUNTRY	FILING DATE	PATENT NUMBER	STATUS	EXP. DATE
USA	08/08/1991	5,250,549 5,292,758	Issued	08/08/2011 08/08/2011
Germany	08/07/1991	EP 472,053	Issued	08/07/2011
United Kingdom	08/07/1991	EP 472,053	Issued	08/07/2011
France	08/07/1991	EP 472,053	Issued	08/07/2011

CONFIDENTIAL
JH 008150

-50-

EXHIBIT 12.2(f)

COMMUNICATIONS

With respect to ABT-594, Abbott has received the following communications:

- * Correspondence from Sibia Neurosciences, 505 Coast Blvd. South, Suite 300, La Jolla, CA 92037 (Sibia was acquired by Merck & Co., Inc. in August, 1999) including, most recently, a letter dated March 13, 1998.
- * Correspondence from ICT Pharmaceuticals c/o Stadheim and Gear, Ltd., 400 North Michigan Ave., Chicago, IL 60611 including, most recently, a letter dated September 14, 2000.

The Sibia and ICT correspondence each refer to their patents on research tools.

CONFIDENTIAL
JH 008151

-51-

EXHIBIT 12.2(i)

Compound Reports

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JH 008152

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ABT - 773

Descriptive Memorandum

February 2001

Abbott Laboratories

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JH 008153

ABT-773*Opportunity Overview*

ABT-773 pertains to a promising new class of antibiotics known as ketolides. ABT-773 is likely to have activity against resistant strains of bacteria and will, therefore, compete effectively against currently marketed antibiotics. The compound is currently in Phase II/III trials. Phase III clinical trials began in Q4, 2000. ABT-773 has an expected U.S. launch date in Q1, 2004. Ex-U.S. launches are projected in 2004 for Europe and Japan.

Product features such as high efficacy, activity against resistant strains of bacteria and convenience should enable it to compete against both Zithromax and newer agents such as the quinolones. Dosing is expected to be once-a-day. A 5-day convenience pak at a competitive price will help maximize sales.

The US Market

The overall antibiotic market in the U.S. reached \$8.9 billion in sales in 1999. The tab/cap segment is the largest; sales in 1999 were \$5.7 billion. The I.V. and oral suspension segments are comparatively smaller; total sales topped \$2.1 and \$1.1 billion, respectively.

Tab/cap and oral suspension prescription volume had been declining 1-2% per year in the period of 1995-1998, due to more appropriate prescribing in the face of increasing resistance. However, total tab/cap prescription volume recovered in 1999 and grew 6.3%. Even in the face of negative pressure on antibiotic use, dollar sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics. The market is willing to bear higher costs for agents that satisfy unmet needs. The I.V. market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

Macrolides, largely fueled by the gains of Zithromax, have seen significant growth in terms of both prescriptions and sales. Zithromax prescriptions far outnumber those of other competitors, while its sales have nearly surpassed those of the sales leader, Cipro. Historically, quinolones saw relatively limited use for community respiratory tract infections (RTIs) because of poor Gram-positive coverage and sub-optimal adverse event profiles. Newer quinolones such as Levaquin have been successful in achieving more widespread use by virtue of its improved activity and adverse event profile. Levaquin currently accounts for approximately 30% of the quinolone market share. It is anticipated that recent quinolone introductions (Avelox, Tequin) will build upon the RTI momentum established by Levaquin. The growth of the macrolide and quinolone classes has come largely at the expense of cephalosporins and generic agents such as erythromycin and penicillin.

The following table shows 1999 tab/cap sales and prescriptions by class/product:

	Sales			TRXs		
	Sales (\$MM)	Share	CAGR ₉₅₋₉₉	TRXs (MM)	Share	CAGR ₉₅₋₉₉
Penicillins	\$148.3	2.6%	-1.0%	52.5	23.7%	-5.6%
Cephalosporins	\$980.9	17.2%	-5.8%	37.9	17.1%	-3.5%
Cefin	\$383.9	6.7%	1.8%	5.0	2.3%	-1.0%
Ceftiz	\$188.7	3.3%	12.5%	2.7	1.2%	11.3%
Other	\$508.3	7.1%	-14.7%	39.1	13.6%	-4.8%
Ext. Spec. Macrolides	\$1,595.6	27.9%	19.9%	36.1	16.3%	20.8%
Biaxin	\$690.5	12.1%	6.1%	11.3	5.1%	1.2%
Zithromax	\$891.1	15.6%	42.1%	24.4	11.0%	41.5%
Other	\$14.0	0.2%	21.9%	0.4	0.2%	53.0%
Quinolones	\$1,622.1	28.4%	17.0%	24.0	10.8%	11.7%
Cipro	\$902.5	15.8%	8.3%	14.1	6.4%	5.1%
Levaquin	\$529.4	9.3%	NA	7.0	3.1%	NA
Other	\$190.2	3.3%	-2.2%	3.0	1.3%	-6.4%
Avsomanlin	\$778.1	13.6%	17.8%	10.7	4.8%	11.8%
Other Classes	\$599.5	10.3%	-1.7%	60.4	27.3%	-4.1%
TOTAL TAB/CAP	\$5,715.4	100.0%	8.9%	221.5	100.0%	0.1%

U.S. Market Projections

Resistance to antibiotics is likely to increase, creating opportunities for new agents with activity against resistance. Physicians will be urged to choose agents with an appropriate spectrum of activity relative to the infection being treated. Resistance will increasingly become part of the promotional mix for emerging agents. The ability of an agent to treat resistant strains and the real or perceived ability to slow or prevent resistance development (mutation prevention concentration, low mutation frequency, structure-activity relationships, etc) may confer competitive advantage to such agents.

- Quinolones, which historically have seen limited use in community-acquired respiratory infections, will become a significant class in this segment as new agents from this class are launched that specifically target RTIs.
- The market will become more competitive as new agents enter both the community segment (ketolides, quinolones) as well as the nosocomial segment (oxazolidinones, streptogramins, everninomycins, peptides, others).
- Several key branded antibiotics will lose patent exclusivity over the next three to five years.. This may create an opportunity in the pediatric market as the top three pediatric brands (Augmentin, Cefzil, Zithromax) are among those losing patent exclusivity.

Antiviral influenza and cold therapeutics, as well as an increasing number of antibacterial vaccines may have a negative impact on antibiotic prescriptions.

The Ex-U.S. Market

Ex-U.S. sales of antibiotics totaled \$11.7 billion in 1999. Tab/cap represents the largest segment, with sales of \$9.4 billion from 770 million total prescriptions. Total Rx growth has been flat, with a 1996-99 CAGR of 0.5%. The use of antibiotics is predicted to slowly decline due to more judicious use of antibacterials in the face of increasing bacterial resistance.

Ex-U.S., the quinolone class accounted for 8% of total tab/cap market prescriptions (62 million Rx's) and 13% of sales (\$1.2 billion). Ciprofloxacin is the market leader ex-U.S. with approximately 47% of the quinolone market Rx's (29 million Rx's) and 44% (\$530MM) of sales. Levofloxacin launched in many European markets in 1998/1999 and holds approximately 14% Rx share of the European quinolone market and 0.8% of the overall tab/cap market. Although grepafloxacin and trovafloxacin also launched in some European countries in 1999, both products were recently pulled from the market due to liver toxicity and other complications. Moxifloxacin launched in Germany in Q4 1999, but has not yet been approved in other markets. In Japan, levofloxacin launched in 1994 and still commands a 65% Rx share of the quinolone market and 10% of the Japanese tab/cap market overall. Japan accounts for approximately 80% of ex-U.S. levofloxacin sales (\$370MM).

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Scientific Rationale for ABT-773

The likely profile of ABT-773 justifies further development:

- ABT-773 pertains to a new class of antibiotics.
- Good activity against resistant Gram + organisms, particularly macrolide-resistant *S. pneumoniae*.
- Convenience, safety, and tolerability profile competitive with Z-pak.
- Oral Suspension and I.V. forms enabling penetration into pediatrics and hospital segments.

Clinical Studies

The safety and efficacy of ABT-773 in AECB were studied in a multi-center Phase II clinical trial conducted between January and April of 1999. Dosing regimens of 100mg TID and 200mg TID were tested. Of the 169 enrolled patients, 159 were clinically evaluable and 96 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 100mg TID	ABT-773 200mg TID	Overall Eradication
<i>S. pneumoniae</i>	100% (13/13)	90% (9/10)	96% (22/23)
<i>M. catarrhalis</i>	100% (6/6)	100% (7/7)	100% (13/13)
<i>H. influenzae</i>	96% (23/24)	92% (24/26)	92% (47/50)
<i>H. parainfluenzae</i>	100% (6/6)	88% (7/8)	93% (13/14)

Clinical Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (77/80)	92% (73/79)
Failure	4% (3/80)	8% (6/79)

Clinical and Bacterial Response	ABT-773 100mg TID	ABT-773 200mg TID
Cure	96% (46/48)	94% (45/48)
Failure	4% (2/48)	6% (3/48)

Adverse Events	ABT-773 100mg TID	ABT-773 200mg TID	Overall
Taste Perversion	5% (4/84)	8% (7/85)	6.5% (11/169)
Diarhea	11% (9/84)	6% (5/85)	8% (14/169)
Nausea	2% (2/84)	2% (2/85)	2% (4/169)
Abdominal Pain	1% (1/84)	2% (2/85)	2% (3/169)
Headache	2% (2/84)	1% (1/85)	2% (3/169)
Rash	2% (2/84)	1% (1/85)	2% (3/169)
Dyspnea	2% (2/84)	-	1% (2/169)
Elev. Liver Funct. Test	1% (1/84)	1% (1/85)	1% (2/169)
Fever	-	2% (2/85)	1% (2/169)

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The safety and efficacy of ABT-773 in AECB were studied in a multi-center Phase IIb clinical trial from October 1999 to March 2000. Doses of 150mg QD, 300mg QD, and 600mg QD were tested. Of the enrolled subjects, 342 were clinically evaluable, and 169 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 150mg QD		ABT-773 300mg QD		ABT-773 600mg QD		Overall Eradication
<i>S.pneumoniae</i>	83%	(10/12)	90%	(9/10)	100%	(13/13)	91% (32/35)
<i>M.catarrhalis</i>	80%	(8/10)	92%	(12/13)	91%	(10/11)	88% (30/34)
<i>H. influenzae</i>	94%	(17/16)	89%	(17/19)	83%	(19/23)	88% (53/60)
Clinical Response							
Cure	87%	(98/113)	90%	(105/117)	90%	(101/112)	
Failure	13%	(15/113)	10%	(12/117)	10%	(11/112)	
Clinical & Bacteriological Response							
Cure	84%	(42/50)	88%	(49/56)	94%	(59/63)	
Failure	16%	(8/50)	12%	(7/56)	6%	(4/63)	
Adverse Events							
Taste Perversion	5%	(4/84)	19%	(25/129)	29%	(37/129)	17% (66/384)
Diarrhea	13%	(16/126)	12%	(15/129)	21%	(27/129)	15% (58/384)
Nausea	7%	(9/126)	13%	(17/129)	30%	(38/129)	17% (64/384)
Vomiting	2%	(3/126)	3%	(4/129)	11%	(14/129)	5% (21/384)
Nausea & Vomiting	0	(0/126)	<1%	(1/129)	4%	(5/129)	2% (6/384)
Abdominal Pain	4%	(5/126)	4%	(5/129)	4%	(5/129)	4% (15/384)

The safety and efficacy of ABT-773 in Acute Bacterial Sinusitis (ABS) were studied in a multi-center Phase IIb clinical trial conducted from October 1999 to March 2000. Dosing regimens of 150mg QD, 300mg QD, and 600mg QD were tested. Of the 292 enrolled subjects, 246 were clinically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 150mg QD		ABT-773 300mg QD		ABT-773 600mg QD		Overall Eradication
<i>S.pneumonia</i>	3/3		8/8		9/12		20/23
<i>M. catarrhalis</i>	8/9		3/4		4/4		15/17
<i>H. influenzae</i>	3/5		7/7		5/7		15/19
<i>S.aureus</i>	1/1		1/1		3/4		5/6
Clinical Response							
Cure	89%	(70/79)	83%	(70/84)	71%	(59/83)	
Failure	11%	(9/79)	17%	(14/84)	29%	(24/83)	
Adverse Events							
Taste Perversion	1%	(16/97)	14%	(14/98)	27%	(26/97)	14% (41/292)
Diarrhea	6%	(6/97)	6%	(6/98)	17%	(16/97)	10% (28/292)
Nausea	3%	(3/97)	12%	(12/98)	26%	(25/97)	14% (40/292)
Vomiting	1%	(1/97)	6%	(6/98)	17%	(16/97)	8% (23/292)

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The safety and efficacy of ABT-773 in community-acquired pneumonia (CAP) were studied in a multi-center Phase IIb clinical trial from October 1999 to March 2000. Dosing regimens of 300mg QD and 600mg QD were tested. Of the 187 enrolled subjects, 1248 were clinically evaluable, and 15 were both clinically and bacteriologically evaluable. The following chart summarizes the results.

Bacterial Eradication	ABT-773 300mg QD		ABT-773 600mg QD		Overall Eradication	
<i>S. pneumoniae</i>	87%	(13/15)	100%	(7/7)	91%	(20/22)
<i>M. catarrhalis</i>	75%	(6/8)	50%	(2/4)	67%	(8/12)
<i>H. influenzae</i>	100%	(9/9)	72%	(13/18)	81%	(22/27)
<i>M. pneumoniae</i>	93%	(13/14)	93%	(14/15)	93%	(27/29)
<i>C. pneumoniae</i>	95%	(19/20)	79%	(19/24)	86%	(38/44)
<i>L. pneumoniae</i>	100%	(3/3)	100%	(2/2)	100%	(5/5)
Clinical Response						
Cure	92%	(72/78)	80%	(56/70)		
Failure	8%	(6/78)	20%	(14/70)		
Clinical & Bacterial Response						
Cure	92%	(54/59)	82%	(47/57)		
Failure	8%	(5/59)	18%	(10/57)		
Adverse Events						
Taste Perversion	17%	(16/95)	26%	(24/92)	21%	(40/187)
Diarrhea	14%	(13/95)	19%	(17/92)	16%	(30/187)
Nausea	12%	(11/95)	22%	(20/92)	17%	(31/187)
V omitting	10%	(9/95)	15%	(14/92)	12%	(23/187)

• Appendix 1

Key Emerging Competitors

Generic	Brand	Company	Class	Status
modifloxacin	Avelox	Bayer	Quinolone	Approved by FDA 12/13/00
galifloxacin	Tequin	BMS	Quinolone	Approved by FDA 12/21/00
gemifloxacin	Factive	SKB	Quinolone	Filed NDA 12/15
T-3811	TBD	BMS/Toyama	Quinolone	Phase I
telithromycin	Ketek	Aventis	Ketolide	Filed NDA 3/00
linezolid	Zyvox	Pharmacia	Oxazolidinone	Approved by FDA Q2 '00

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ABT – 627

Descriptive Memorandum

February 2001

Abbott Laboratories

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ABT-627

Opportunity Overview

ABT-627 is an orally bioavailable endothelin antagonist with a high selectivity for the E_{ta} receptor. The endothelins (ET-1, ET-2, ET-3) are a family of 21 amino acid peptides first identified in 1988. Endothelin is a potent, long acting vasoconstrictor produced by vascular endothelial cells. The known biological effect of ET-1 are believed to be mediated principally through the E_{ta} receptor. These include potent and uniquely sustained vasoconstriction of vascular smooth muscle, positive inotropy of myocardium, and the stimulation of cell proliferation or the hypertrophy in vascular smooth muscle cells, cardiac myocytes, and fibroblasts.

In vitro studies in cultured cells have established that ABT-627 selectively binds to the E_{ta} receptor, and that ABT-627 is a potent inhibitor of ET-1 binding to the E_{ta} receptor.

Studies in cultured human prostate cancer cells and other cultured cells have shown that ABT-627 acts as a functional antagonist of ET-1, and these effects have been confirmed in vivo by assessing the effect of ABT-627 on the ET-1 induced pressor response in rats. Further animal studies have suggested that oral ABT-627 may be effective in the treatment of congestive heart failure, pulmonary hypertension, hypertension, arterial restenosis, and myocardial infarction.

In addition to literature and animal models supporting the role of endothelin antagonists in cardiovascular indications, data exists supporting the role of the ET-1 cytokine as a pathogenic mediator in cancer.

The current role of endothelin in the manifestations of metastatic prostate cancer (PCA) and other tumors have yet to be fully defined. However, Abbott scientists and thought leaders have made multiple observations about endothelin biology which suggest that endothelin may play a role in the biology and pathophysiology of metastatic prostate disease and other metastatic disease such as ovarian, cervical and renal tumors.

ABT-627 has successfully completed Phase II trials for PCA, and the results demonstrate efficacy in hormone refractory PCA. The end of Phase II meeting with the FDA was held on October 4th. The data from Phase II was very favorably received and "best package" comments were made. Fast track designation and rolling NDA were granted. The FDA was conceptually in agreement with preliminary design of Phase III clinicals and clinical end points to measure. While not a dictate, a second Phase III trial will likely be conducted to insure the best opportunity for a successful outcome. The Phase III program is scheduled to commence before year-end. It is expected that filing on ABT 627 will occur in US and ex-US 1Q 2004. The compound is also in Phase I trials for other cancer types. Phase II studies in other cancer types will commence in 2Q04. Other indications outside of oncology are also being considered, to optimize the commercial potential of this asset.

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The US Market

Prostate cancer is the most common cancer to strike nonsmoking men. The NCI estimates that there are over 1.7 million men living with prostate cancer in the U.S., and another 179,300 will be diagnosed in 1999. Nearly 80% of these cases are men over 60 years of age. It is estimated that the prevalence of prostate cancer is 380,000 in Western Europe and 45,000 in Japan. While the vast majority of these patients will be identified with potentially curable disease (25% in Stage I and 50% in Stage II) in the U.S., half of these patients will go undiagnosed until late stage disease in W. Europe and Japan. The skewed distribution of diagnosed cases ex-U.S. is largely due to less aggressive prostate cancer screening programs compared to the U.S.

Prostate cancer has seen few additions or innovations in treatment regimens in the past two decades. Treatments remain, in general, radical prostatectomy (RP) for localized disease, radiotherapy for locally advanced disease and hormone therapy for advanced disease. Patients receiving hormone therapy become refractory to this treatment after two to three years, although many will continue on hormone therapy. These hormone refractory prostate cancer (HRPCa) patients usually have a life expectancy of approximately 12 months, and no existing standard of care exists for treating these patients. No therapy has shown a significant impact on survival in these patients, although some chemotherapeutic regimens may offer promise.

There is a general trend toward using hormone therapy in earlier stage patients. In some centers, patients are receiving hormone therapy prior to surgery or radiation, in an attempt to improve outcomes in these definitive treatments. Some thought leaders suggest that this earlier utilization has contributed to the overall mortality improvements in PCA. Studies are ongoing looking at different uses for hormone therapy, including intermittent therapy, in an attempt to improve outcomes and mitigate the morbidity associated with hormonal therapy.

Hormone therapy remains the mainstay of prostate cancer treatment in earlier stages. Chemotherapy, however, has gained additional attention in hormone refractory disease as new combinations and regimens offer the potential for greater therapeutic benefit with fewer side-effects. This trend will take several years before clinical trials are completed and community based oncologists adopt these regimens, so the current cytotoxic market in PCA is small.

The total dollar growth of this market has slowed as the two market leaders, Lupron (leuprolide/TAP) and Zoladex (goserelin/Zeneca), have experienced increased price pressures from managed care and Medicare. About half the states are currently reimbursing these therapies at a least cost option (only paying for the cheapest alternative), putting downward price pressures on Lupron (\$6,500/yr) to match Zoladex's (\$4,500/yr) lower price point. Thus, US Lupron dollar sales declined between 1997 and 1998, despite an increase in patient volume.

Growth has also stagnated due to a lack of innovation in this hormone dominated category. There have been few therapeutic advances in the treatment of PCA in the last 5 years.

The only chemotherapy approved for use in HRPCa patients with pain is Novantrone (mitoxantrone/Immunex), but the marginal benefits this compound delivers is deeply undercut by its severe toxicities and a lifetime cap on dose. Novantrone and steroids significantly reduced the metastatic pain in 40% of patients, but it does not appear to provide a survival advantage. Novantrone is dosed by I.V. infusion every 21 days, at a cost of \$560 per treatment, or an annual cost of around \$8,000. Use of this agent is associated with significant side-effects, including myelosuppression, cardiac toxicity (which limits dosing) and nausea. It is this negative side-effect profile that inhibits the use of this agent in more patients. Only about 4% of U.S. HRPCa patients received Novantrone therapy in 1998. Novantrone has not been approved ex-US.

Only about 17% of HRPCa patients received any chemotherapy in 1998. The most common drugs included estramustine, paclitaxel and eloposide. These drugs continue to be some of the most studied compounds in HRPCa ongoing research and represent the greatest short-term promise in the cytotoxic treatment of this advanced disease state.

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US Sales of Products to Treat Prostate Cancer

Product	1997 Dollar Sales (MM)	1998 Dollar Sales (MM)	% chng '97-'98
Lupron (leuprolide/TAP)	\$650	\$667	2.6%
Zoladex (goserelin/Zeneca)	233	296	27.3
Casodex (bicalutamide/Zeneca)	58	68	17.24
Euflexin (flutamide/Schering)	74	67	-9.5
Novantrone (mitoxantrone/Immunex)	33	35	6.1
Nilandrone (nilutamide/Hoechst)	12	24	100
Emcyt (estramustine/Pharmacia/Upjohn)	8	14	75
Taxol (paclitaxel/BMS)	4	8	100
Veliposid (etoposide/BMS)	5	4	-20
Others	27	31	14.8
Total	1,104	1,214	10%

Source: Tandem Research and Price Probe

US Market Projections

- Novantrone (mitoxantrone/Immunex) is currently the only product approved for the treatment of hormone refractory PCA with pain. It currently falls short on the market needs in terms of efficacy and side-effect profile.

Attribute	Novantrone Profile
Dosing	I.V. infusion cycles
Cost	Expensive, ~\$10,000/yr
Efficacy	Provides marginal improvements in quality of life
Reimbursed	Yes
Side-effects	Dose limiting toxicities
Promo Efforts	108 oncology reps
Targets	Oncologists

Several surveys indicate that there are over 100 compounds in preclinical and clinical development for prostate cancer and various solid tumors. The compounds listed in the appendix represent compounds that appear to offer the greatest promise and/or potential for competition for ABT-627. However, since the most likely use of ABT-627 will be in combination with best therapy, it is difficult to define the extent of competitive threat that any of these compounds represent. In general, other cytostatic agents probably offer the greatest threat as a replacement for ABT-627. However, even other cytostatic agents may be combined to maximize the activity of the various mechanisms.

To date, PPD is aware of only one other endothelin receptor antagonist in development for cancer, from Yamanouchi, which began Phase I studies in the Fall of 1999. ABT-627 is still poised to be the first endothelin receptor antagonist to reach the market for oncology.

Scientific Rationale for ABT-627

There are relatively low hurdles for entry for a product to treat hormone refractory prostate cancer, as no truly effective agents presently exists. Quality of life is paramount in this population, followed by improvements in disease progression and survival. Quality of life parameters could include an impact on pain/or delay in pain onset or other performance type measures of daily activities. As all hormone therapy ultimately fails, a product that delays disease progression is needed.

Unmet Need	Pipeline Impact
Improvements in QOL	<ul style="list-style-type: none"> ABT-627's profile goal is to provide improvements to a patient's QOL or blunt a decrease in QOL Cytotoxic agents rarely have significant positive impacts on QOL Other cytostatic agents may offer this benefit
Improvements in survival	<ul style="list-style-type: none"> It is unlikely that improvements in survival will be seen in our current trials Cytotoxic agents may offer a survival advantage, perhaps in combination with ABT-627
Improvements in time to disease progression	<ul style="list-style-type: none"> Cytostatic and cytotoxic agents offer the greatest promise for this benefit

Our objective is to provide physicians and patients with a novel option for the treatment of hormone refractory prostate cancer, distinguish ABT-627 from current cytotoxic therapies and encourage the treatment of advanced prostate cancer patients currently only receiving hormonal therapy.

ABT-627 will be positioned as a physician and patient-friendly choice for advanced prostate cancer patients who have failed hormone therapy. ABT-627's novel mechanism of action provides a delay in disease progression and a positive impact on QOL. The oral, QD dosing enhances compliance and minimizes disruptions to daily living.

The message will focus on 3 key attributes:

- Efficacy (defined as increased time to tumor progression) in a patient group with few options
- Improvements in quality of life
- Convenience

Physicians no longer have to choose between *treating* advanced prostate cancer patients and a patient's quality of life. ABT-627 has a positive impact on disease progression and symptoms associated with quality of life, without the baggage of significant side-effects or the inconvenience of parenteral administration associated with current therapy choices.

This message expresses the key features of the agent in terms of patient benefits, as opposed to emphasizing the scientific/clinical aspects. Since prostate cancer is a terminal disease with a relatively long time for disease progression, the quality of a patient's life becomes even more critical. Especially in cancer treatment, where the therapy can often feel worse than the disease, the benefits that ABT-627 will bring, coupled with its benign side-effect profile, will have a significant impact on prostate cancer patients' lives.

Clinical Studies

Phase II trials have been completed and the data are being analyzed. Preliminary results for the primary endpoint of time-to-disease progression and the secondary endpoint of time-to-PSA progression show that ABT-627 favorably delays both phenomena with a benign adverse event profile. The results are summarized below.

Disease Progression: The delay in median time-to-disease progression for evaluable subjects was improved by 52% and 43% for the 10mg and 2.5mg doses respectively over the placebo time-to-disease progression of 4.3 months.

Time-to-PSA Increase: A 150% and 150% improvement in median time-to-PSA progression for evaluable subjects was observed for the 10mg and 2.5mg doses respectively over the time-to-PSA progression placebo of 2 months.

Significant dose related decreases were observed in markers of metastatic bone disease.

Key Prostate Cancer Competitors

Product	Company	Phase	Projected NDA Filing	Description	Anticipated Impact on ABT-627
AG 3540	Agouron	III	2000	MMPI	In combination with mitoxantrone/prednisone. Unknown impact.
Marimastat	British Biotech	II	2001	MMPI	Side-effect profile significantly worse than ABT-627. Probably minimal impact.
SU 101	Sugen	III	2002	PDGF TK antagonist	Phase III in combination with mitoxantrone set to start in 1999. Uncertain impact.
AR 623	Aronex	II	2002	All-transretinoic acid	IV liposomal form of ATRA. HRPc trial began November 1998. Probably additive.
MGI 114	MGI Pharma	II	2002	Abylating agent	Lead compound in acylfuvenes. Fairly toxic. Probably additive.
Liposomal Encapsulated doxorubicin	NeoPharm and P&U/Alza and others	II	2002	Anthracycline	Various forms being developed by various companies. Probably additive.
Satraplatin	BMS	III	2000	Platinum complex	Oral platinum analog w/toxicities comparable to carboplatin. Probably additive.
Taxol	BMS	II	2001	taxane	In various combinations with other chemo agents. Probably additive.
Taxotere	RPR	II	2001	taxane	In various combinations with other chemo agents. Probably additive.

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ABT-594

Descriptive Memorandum

February 2001

Abbott Laboratories

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ABT-594 Opportunity Overview

ABT-594 is a non-opioid, non-NSAID analgesic that is a potent and selective neuronal nicotinic receptor (NNR) agonist being studied for the treatment of pain. ABT-594 is 30 to 100-fold more potent and equally efficacious to morphine in several well-characterized animal models of pain. The preclinical side effect and dependency liability profile of ABT-594 is superior to that of morphine.

ABT-594 is orally administered, and BiD dosing is expected. Its initial targeted indication is symptomatic treatment of diabetic neuropathic pain. It is covered by a composition of matter patent through June of 2016, and also has a use patent pending in analgesia that would provide protection through September of 2017.

The IND filing of ABT-594 was in December 1998. A Phase IIb (dose ranging) trial began April 2000 in diabetic neuropathic pain. A Go/No Go decision for clinical efficacy is expected June 2001. The NDA filing is expected in 3Q2003. Development of additional formulations is under consideration (parenteral, transdermal, extended-release).

U.S. sales in 1999 for the key neuropathic pain treatments, Neurontin, carbamazepine, and tricyclic antidepressants (TCAs), are estimated to be \$350 million. Neurontin sales account for the bulk of this, with an estimated 40% of this antiepileptic drug's sales being for neuropathic pain. Neurontin's 2000 sales are expected to reach \$1 billion with perhaps 50% of its use in neuropathic pain. This dollar market value likely underestimates this market's potential due to a number of factors. Only the anticonvulsant, Tegretol (carbamazepine), currently off patent, and Lidoderm, a lidocaine patch, have specific indications for a type of neuropathic pain (trigeminal neuralgia and post-herpetic neuralgia, respectively) in the U.S. Currently, there is an unmet market need for novel neuropathic pain treatments such as ABT-594. Therefore, this compound is likely to be well received in this arena. Outside the U.S., Neurontin recently received an indication in the U.K. for the treatment of neuropathic pain. Despite these opportunities, there has been little to no funding from the pharmaceutical industry to improve diagnosis and treatment of neuropathic pain and drive market growth.

Ex-U.S. sales of carbamazepine and Neurontin for treatment of neuropathic pain are estimated to be approximately \$140MM in 1999. Carbamazepine is still the treatment of choice ex-U.S., with estimated sales of approximately \$90MM in neuropathic pain. Neurontin has achieved only \$53MM in sales for this pain segment, with a price approximately 3-4 times that of carbamazepine, suggesting a patient share of only 10-20%.

Nociceptive pain is categorized by duration (acute or chronic) and by severity (mild, moderate, and severe). The mild and, to a lesser extent, moderate segments have multiple product entries and are generally well satisfied by OTC products such as aspirin, acetaminophen and ibuprofen. The prescription market for nociceptive pain is made up of four key classes of analgesics: NSAIDs, COX-2s, Opioids (and combination products), and Other Non-Opioids. In 1999, sales for these four classes of analgesics exceeded \$12BB (\$6.7BB U.S., \$5.6BB Ex-U.S.)

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Market Size / Prevalence

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. Chronic pain, including both neuropathic and nociceptive pain, is considered to be the single most common cause of suffering and disability in the industrialized world with an estimated 25-30% of the population experiencing some form of chronic pain.

Neuropathic pain is a frequent sequela of diabetes, cancer, AIDS and other viral infections, as well as entrapment neuropathies such as carpal tunnel syndrome. Diabetes and its associated complications are increasing at an alarming rate in the United States. Despite advances in treatment, the development of diabetic complications such as neuropathy remains significant. The diagnosed prevalence of diabetic neuropathy is estimated to be about 2 to 3 million patients, with at least 10 to 20% of those patients experiencing painful symptoms (~200,000 to 600,000.) AIDS-related neuropathic pain is estimated to affect approximately 40% of HIV-infected individuals (~14 million.) Post-herpetic neuralgia (PHN) is another virally induced neuropathic pain syndrome. Annually, acute herpes zoster infection (shingles) occurs in almost a quarter of a million people over the age of 60 in the U.S. alone. Pain lasting more than one year has been reported in 22% of patients over the age of 55 and in 48% of those over 70 years of age. In cancer, nerves can be damaged by mechanical distortion from a tumor mass, infiltration by tumor, chemotherapy, or radiation therapy and, therefore, neuropathic pain is common. An estimate of the prevalence rate for cancer-related neuropathic pain in the U.S. is 200,000 people.

Chronic nociceptive pain categories include osteoarthritis (OA), chronic back and neck pain, rheumatoid arthritis (RA), and cancer pain. These diagnoses are expected to become more prevalent as the population ages. Current overall prevalence for these disorders is staggering (over 200 million worldwide) and, although the diagnosed and treated populations are lower, improved treatment options and awareness have the potential to drive significant growth. OA is one of the most common nociceptive pain conditions treated by primary care physicians and three-fourths of OA sufferers surveyed indicate that the disease interferes with their daily activities. Chronic back and neck pain are also highly prevalent and represent an estimated 40% of a primary care physician's (PCP's) chronic pain patient population.

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Competition, Current Marketed Products:

The following tables show the factored U.S. and ex-U.S. prescription and sales volume for key neuropathic pain therapies in 1999.

1999 Key Neuropathic Pain Products, Estimated TRxs				
Product/Class	1999 U.S. TRx (MM)	U.S. TRx CAGR '97-'99	1999 ex-U.S. TRx (MM)	ex-U.S. TRx CAGR '97-'99
Neurontin	3.3	26.3%	N/A	N/A
carbamazepine	1.0	12.6%	N/A	N/A
TCAs	8.2	1.1%	N/A	N/A
TOTAL	12.5	5.6%	N/A	N/A
Source: IMS, factored for neuropathic uses.				
N/A = not available				

1999 Key Neuropathic Pain Products, Estimated \$ Sales				
Product/Class	1999 U.S. Sales (\$MM)	U.S. Sales CAGR '97-'99	1999 ex-U.S. Sales (\$MM)	ex-U.S. Sales CAGR '97-'99
Neurontin	\$308	28.7%	\$53	57.6%
carbamazepine	\$17	13.1%	\$87	2.5%
TCAs	\$26	-3.3%	N/A	N/A
TOTAL	\$351	21.7%	\$140	10.1%
Source: IMS, factored for neuropathic uses; Ex-U.S. data includes retail pharmacy data from all audited markets				
N/A = not available				

Competition, Products in Development

Almost 100 compounds are currently in development for prescription pain management, though some of these compounds are also being developed for non-analgesic indications. Most of the analgesic compounds in the pipeline represent incremental improvements over the opioids or NSAIDs, or consist of new formulations or delivery mechanisms for the standard analgesics. Fewer than 30% of the compounds in development have novel mechanisms of action. Drugs with novel mechanisms are expected to provide the bulk of promoted competition for ABT-594.

In addition to the novel analgesics in the table below, a number of new formulation and combination products, most often containing an opioid, are in development. Second generation COX-2s are also in development but are not likely to represent major breakthroughs on the scale of the first generation products.

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Analgesia Development Pipeline – Key Novel Agents				
Product	Company	Mechanism	Phase	Comments
pregabalin	Pfizer	Unknown; possibly through (2 nd subunit binding	III	Neuropathic pain; chronic pain, follow-up to Neurontin
saredutant	Sanofi	NK-2 receptor antagonist	II	General pain; MOA losing favor; active program
ZD4952, ZD 6416	Zeneca	Prostaglandin receptor antagonist	II	Moderate to severe pain, neurogenic pain
GV196771	Glaxo	Glycine antagonist	II	Chronic pain; showing promise
Tepoxalin	Johnson & Johnson	COX/5-LO inhibitor	II	OA, described as 'steroid replacing anti-inflammatory drug'
darbufelone	Parke-Davis	COX/5-LO inhibitor	II	General pain
117mSn DTPA	Brookhaven National Lab/Diatide	Unknown	II	Cancer pain Bone cancer (preclinical)
cizolirtine	Esteve	Substance P agonist	II	Analgesia, antipyretic
ADD 234037/ harkoseride	Houston University	Glycine NMDA associated antagonist	II	Neurogenic pain
LY303870/ lanepitant	Eli Lilly	Neurokinin 1 antagonist	II	Pain (migraine – discontinued)
colykade devacade	Merck	Cholecystokinin B antagonists	II	Pain (UK)
RPR 100893 dapitant	Aventis	Neurokinin 1 antagonist	II	Pain (France)
proseptide TX14A	Myelos Neurosciences	Unknown	III	Diabetic neuropathies, Pain
CNS 5161	Cambridge NeuroScience	Glutamate antagonist, NMDA receptor antagonist	I	Neurogenic pain
HCT-3012	NicOx	Nitric oxide NSAID	I	Pain and inflammation
Sources: ADIS, IMS, Decision Resources, company reports				

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Analgesia Development Pipeline – Nicotinic Mechanisms			
Product	Company	Phase	Comments
GTS-21	Taisho	II	Target is Alzheimer's disease; may have preclinical pain program; looking for partner
CMI 980	Cytomed	Preclinical	Target is pain; epibatidine analog
SIB-T1887	Sibia	Preclinical	Target is pain
FID 072021	Fidia	Preclinical	Target is pain; not actively funding
Sources: ADIS, IMS, company reports			

Unmet Needs

In general, a significant unmet need exists for safer, non-abusable, non-addicting, non-tolerance-producing, and non-scheduled efficacious oral and parenteral analgesic products for the treatment of moderate to severe neuropathic and chronic nociceptive pain.

Unmet Market Needs and the Impact of the Pipeline	
Unmet Need	Pipeline Impact
Efficacy in moderate to severe pain without tolerance, dependence or abuse potential	Novel nicotinic agents like ABT-594 may provide efficacy in more severe pain states without opioid-like liabilities.
Efficacy in neuropathic pain	Pregabalin may provide incremental improvement in neuropathic pain efficacy over gabapentin, but may also have increased frequency of adverse events. Novel nicotinic agents like ABT-594 appear to have efficacy in neuropathic pain, based on animal models.
Reduction in the GI bleeding risk of NSAIDs	COX-2 inhibitors appear to reduce the incidence and severity of GI ulcers and bleeding; second generation COX-2s may increase therapeutic window further; ABT-594 may need to demonstrate low G.I. complication rate.
Overcome ceiling effect of NSAIDs	Preclinical studies did not indicate a ceiling effect for novel nicotinic agents like ABT-594.
Extended dosage intervals or novel delivery mechanisms for improved compliance and convenience	Once weekly dosing formulations being explored for COX-2s, etc. Transdermal patch technology improvements likely; may need to provide line-extension / alternate formulations for ABT-594.
Therapies aimed at disease modification, prevention	Agents that decrease rate of diabetic complications (e.g., aldose reductase inhibitors) or directly treat neuropathy (bimoclomol) may decrease incidence of neuropathic pain; thereby decreasing available market for ABT-594.

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Product / Development Background

Scientific Rationale for ABT-594

Recent findings in the understanding of pain mechanisms have led to new conceptual approaches to clinical pain and a new understanding of potential novel molecular targets for analgesic drug development. Molecular targets have included modulators of glutamate neurotransmission (NMDA antagonists), ion channel modulators (neuron specific calcium channels, TTX-resistant sodium channels), neurokinin antagonists (NK-1), and novel anti-epileptics targeting the calcium receptor. None of these approaches has yet produced compounds exhibiting broad-spectrum analgesic efficacy with decreased side effect liability.

ABT-594 is a non-opioid, non-NSAID analgesic that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of pain. The preclinical side effect and dependence liability profile of ABT-594 is superior to that of morphine. Mechanistically, ABT-594 is a potent and selective neuronal nicotinic receptor (NNR) agonist with high oral bioavailability in rat, dog, and monkey.

In pre-clinical studies, ABT-594 rapidly distributes to the brain following systemic administration and, like morphine, can work at multiple levels in the central and peripheral nervous system to modulate pain perception. ABT-594 produces antinociceptive effects by interacting at both central and peripheral nAChRs. Injections of ABT-594 into brain at doses 1000-fold lower than given peripherally produce marked antinociceptive activity, indicating that ABT-594 can also activate descending pathways from the CNS to modulate pain processing. It also inhibits the release of the primary nociceptive transmitters, substance P and calcitonin gene related peptide (CGRP) *in vitro*, at the level of the dorsal horn of the spinal cord suggesting that ABT-594 can attenuate mechanisms leading to neurogenic inflammation, central sensitization and consolidation of pain-mediated neuronal changes.

ABT-594 is expected to be a highly differentiated product. It is expected to be the first neuronal nicotinic receptor agonist to receive an indication for pain. It has a novel mechanism of action and a potentially broad coverage of chronic pain conditions. In addition, it has an opioid-like efficacy without tolerance, dependence or abuse potential, while having equivalent/superior efficacy to other drugs used to treat neuropathic pain.

Clinical Studies

Human clinical trials began in 1997. Phase I trials with an oral solution formulation indicated that 150ug/day would be the maximum tolerated dose. Results from subsequent phase I and phase II trials with soft elastic capsule (SEC) and hard gelatin capsule (HGC) suggest that higher doses would be tolerated. Phase IIa studies with ABT-594 SEC formulation suggest a trend towards analgesic effect at 75ug BID, the maximum dose studied in this protocol. ABT-594 was generally well tolerated in these studies. The most common adverse events for subjects receiving ABT-594 75ug BID were nausea (15%), headache (13%), dizziness (7%), insomnia (6%), and vomiting (5%).

A phase IIb study for neuropathic pain at higher, titrated doses of ABT-594 began in April 2000, and ends in June 2001. A total of 320 patients is anticipated to be included in the study.

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Considerations

Target Profile:

The current status of ABT-594's profile vs. target profile is summarized in the table below:

Target Profile Attribute	Probability
Not scheduled (DEA)	High
Very few abnormal Liver Function Tests	High
Few Drug Interactions	High
BID / TID dosing	High
No reduced efficacy or increased AEs in nicotine users	High
Onset of action 1.5 - 2.0 hours	High
Neuropathic efficacy	Medium
No tolerance, dependence or withdrawal	Medium
Other safety OK	Medium
No cravings in ex-nicotine users	Medium
Low nausea / vomiting	Low

Label Strategy:

BASE: Indicated for the treatment of diabetic neuropathic pain.

UPSIDE:

- 1) Treatment of pain associated with OA
- 2) Treatment of post-herpetic neuralgia
- 3) Treatment of neuropathic pain
- 4) Treatment of chronic pain
- 5) Treatment of cancer pain

Cost of Goods Sold:

The projected average daily dose is expected to be a maximum of approximately 600 mcg base equivalent / day. Based upon this dosage projection and the estimated cost of bulk drug substance of \$40M per Kg base equivalent, the estimated cost for drug substance at launch will be approximately \$0.024 per day.

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Pricing:

US: Pricing new, and particularly novel, products at a reasonable premium will likely continue to be the norm in the years leading up to the launch of ABT-594. Current forecast assumptions put the price of ABT-594 at a level comparable to Celebrex and Neurontin, grown at a modest 2% per year to launch year AWP of approximately \$95 for a 30 day prescription.

Ex-US: New pain medications must demonstrate a true advantage in efficacy and/or side effects to receive regulatory approval, especially by the European Medicines Evaluation Agency (EMA); assuming the target efficacy and tolerability profile of ABT-594 is achieved, ABT-594 would meet this requirement. Because ABT-594 may have application in both neuropathic and chronic nociceptive pain, the ex-U.S. pricing assumption for ABT-594 is comparable to COX-2 pricing. The current average price for COX-2's is approximately \$1.10 per day; however, this reflects a large percentage of sales in "free-pricing" countries, where COX-2s launched first, which tend to have higher than average prices. Therefore, the average ex-U.S. price for ABT-594 is assumed to be \$0.90/day.

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ABT - 751

Descriptive Memorandum

February 2001

Abbott Laboratories

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ABT-751

Opportunity Overview

Cytotoxic agents and hormones constitute the dominant classes of drugs available to treat cancer and are responsible for 96% of the total market. Since 1993, Taxol, a taxane developed and marketed by BMS, has been widely used. Another taxane, Taxotere, developed and marketed by Aventis, was launched in 1996. Combined worldwide sales of these two products were of nearly \$2 Billion US in 1999. Clinically, the development of drug resistance is the primary factor that limits the efficacy achievable with these drugs.

Abbott's anti-mitotic agent (ABT-751) is a novel, oral cytotoxic agent that acts by a mechanism similar to that of the taxanes but retains activity against taxane resistant cells. ABT-751 binds to the colchicine site on tubulin and inhibits the *in vitro* polymerization of microtubules. The interference with normal microtubule dynamics leads to a block in the cell cycle at the G2/M phase that ultimately results in the induction of cellular apoptosis. ABT-751 is a potent antimitotic agent that inhibits the proliferation of a broad spectrum of human tumor derived cell lines including those that are paclitaxel and doxorubicin resistant due to the multidrug-resistant (MDR) phenotype or other genetic changes.

ABT-751 demonstrated impressive oral antitumor activity when evaluated in both syngeneic and human xenograft tumor models. The antitumor response was independent of the MDR status of the model, consistent with the activity observed in cell cultures. In sharp contrast with other cytotoxic drugs, the maximum tolerated dosage of ABT-751, on a q.d. 1-5 schedule, could be administered for an extended period (q.d. 1-21 or q.d. 1-28) resulting in a dramatic enhancement of the antitumor activity. These results suggest that the colchicine site ligands, such as ABT-751, will exhibit a broad spectrum of activity that will be distinct from that of other classes of antimitotic drugs. Oral availability of the compound is high. Taxol and Taxotere, in contrast, have no oral bioavailability.

The most significant finding in toxicology studies was a change in systemic and pulmonary vascular resistance following intravenous infusion of ABT-751 to anesthetized dogs. These effects led to an inverse response in cardiac output. Similar changes were observed following infusion of a structurally unrelated colchicine-site ligand, and therefore most likely represent a class effect. Additional toxicology studies focusing on vascular pathology will be performed to further elucidate this finding.

ABT-751 was administered to patients with advanced cancer in Japan in a Phase I study. Toxicities seen after single doses and 5 days of q.d. dosing were nausea, vomiting, diarrhea, epigastric pain, ileus and peripheral neuropathy. Grade 2 toxicity was peripheral neuropathy and associated paresthesias. Pharmacokinetic analyses showed plasma concentrations equivalent to those that affected systemic resistance and cardiac output in the anesthetized dog study. However, no adverse cardiovascular effects were observed in the Japanese Phase I trial. Evidence of ABT-751 efficacy was exhibited in one patient with uterine sarcoma, one patient with NSCLC after single doses, one patient with gastric cancer and one patient with uterine cervical carcinoma demonstrated decreased tumor markers after repeated dosing.

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The planned initial Phase I study in the U.S. will determine the maximum tolerated dose and dose-limiting toxicities of ABT-751 given orally once a day or twice daily for multiple cycles in patients with advanced malignancies. In addition, pharmacokinetics in a western population, and optimal dose and schedule will be determined. Phase II studies will be initiated in patients with different cancer types:

- Refractory breast (taxane failures)
- Hormone refractory prostate
- Bladder
- Lung
- Cervical
- Hepatocellular
- Other possibilities: colorectal, sarcoma, renal cell, pancreatic, HNSCC

Cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market

Global Sales by Market Segment (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
Hormone	4,414	4,784	4,884	5,000	5.2%
Cytotoxic	4,278	5,212	6,268	7,300	21.0%
Adjunctive	3,367	3,651	4,166	4,900	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

Sales by Region (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex- US	6,495	7,370	7,896	8,700	10.3%

Source: Datamonitor

This growth of the cytotoxic segment has been driven primarily by the introduction of new, more effective and expensive therapies such as Taxol (paclitaxel/BMS), Gemzar (gemcitabine/Lilly), Taxotere (docetaxel/RPR) and Hycamtin (topotecan/SB). Uptake of these newer agents, however, can be dependent on the cost sensitivity of the local market.

The clinical targets identified for this compound include late stage breast cancer, late stage NSCL cancer (on-label), with late stage ovarian and pancreatic cancer as additional cancer types where efficacy has been demonstrated, but not filed. This product may also be potentially efficacious in cancers such as gastric, colorectal, prostate, bladder, esophageal, hepatocellular (ex US), lymphoma, and leukemia. Targets will be refined as we know more about this compound's in-vivo activity.

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The following tables summarize the key competitive products by indication (US data only):

Late Stage Breast	
Product	Share
Cyclophosphamide/Cytoxan/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	16.25
Paclitaxel/Taxol/BMS	16.11
Trastuzumab/Herceptin/Genetech	11.26

Late Stage NSCL	
Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

Late Stage Ovarian	
Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/Alza	9.14
Cisplatin/Platinol/BMS	7.58

Late Stage Pancreas	
Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Eludex/ICN Pharma	21.0
Leucovorin/	10.7
Cisplatin/Platinol/BMS	4.72

Compounds in Development

ABT-751 induces a mitotic block by binding to the colchicine site on tubulin and thereby affecting tubulin polymerization. There are no currently available drugs which function by the mechanism described above. However, vinca alkaloids and taxanes fall into the broad category of anti-mitotics although they produce the anti-mitotic effect through different mechanisms. The following table summarizes anti-mitotic compounds in development.

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Company	Compound	Indication	Status of compound	Status of project
Colchicine-site ligands				
Oxgene	combretastatin-A4 phosphate	Tumor vasculature	Phase I	active
Tularik	T138607 (phosphate prodrug)	Cancer (unspecified)	Phase I	active
Tularik	T900607	Cancer (unspecified)	Preclinical	active
ICI/CRC	Amphethirile	Cancer (unspecified)	Phase I (abandoned 1988)	inactive
Wellcome Research	1069C	Cancer (unspecified)	Phase I (abandoned 1996)	inactive
NIH	Trimethylcolchicinic acid	Various tumors	Phase I (1990, abandoned)	inactive
Parke-Davis	CI-980	ovarian, colorectal	Phase II (abandoned 2000)	inactive
Vinca alkaloid-site ligands				
BASF	LU103793 (dolastatin 15 analog)	Cancer (unspecified)	Phase II (abandoned)	active
Servier	Vinxalline	Cancer (unspecified)	Phase I	unknown
NCI	dolastatin 10	Adv. Cancers	Phase I	unknown
Teikoku Hormone	TZT-1027 (dolastatin 10 analog)	Cancer (unspecified)	Phase I (Jpn)	unknown
Lilly	LY 355703 (cryptophycin 52)	Cancer (unspecified)	Preclinical	unknown
Takeda	Maltansine	Cancer (unspecified)	Preclinical	unknown
Microtubule stabilizing agents (non-taxanes)				
Soc. Biotech. Res/ Bristol-Myers Squibb	Epothilone	Cancer (unspecified)	Preclinical	active
Bristol-Myers Squibb	eleutherobin	Cancer (unspecified)	Preclinical	active
Pharmacia & Upjohn	sarcodictyins	Cancer (unspecified)	Preclinical	active
Takeda	GS-164	Cancer (unspecified)	Preclinical	active

The novelty of this mechanism offers the promise of differentiation that will diminish the threat from potential competitors. However, this novelty is balanced by the similarity to current mechanisms, such as taxanes and vinca alkaloids, which suggests the promise of clinical efficacy. With the opportunity to be first or second to market with an agent that binds to the colchicine site, the competitive situation seems modest.

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ABT – 492

Descriptive Memorandum

February 2001

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Hancock_ABT 492

ABT 492

Overview

The commercial success of fluoroquinolones such as ciprofloxacin and levofloxacin, along with the desire to further improve the properties of these compounds (microbiological spectrum and safety, for example) has led to fierce competition to identify analogs with superior therapeutic properties. In addition, the development of resistance to present antibiotics will drive a continued need for new agents. Goals for a quinolone antibiotic include broad-spectrum indications equal to trovafloxacin, antibacterial activity comparable to trovafloxacin, tolerability comparable to levofloxacin, oral and intravenous formulations, once daily dosing, length of treatment equal to moxifloxacin, and an acceptable cost of goods. ABT-492, an in-licensed compound from the Wakunaga Pharmaceutical Co., is being developed for evaluation to meet these goals:

The *in vitro* antibacterial activity of ABT-492 was consistently more potent than trovafloxacin against most quinolone-susceptible pathogens, including species responsible for community and nosocomial respiratory tract infections, urinary tract infections, blood stream infections, skin and skin structure infections, and anaerobic infections. The compound has potent activity against multidrug-resistant *S. pneumoniae* (penicillin-, macrolide-, tetracycline-resistant) and retained activity against *S. pneumoniae* strains resistant to other quinolones including trovafloxacin. ABT-492 was also highly active against anaerobes and ciprofloxacin-susceptible *P. aeruginosa*. ABT-492 was as active as trovafloxacin against *C. trachomatis*, indicating good intracellular penetration. Thus, ABT-492 is likely to be a useful broad-spectrum antibacterial agent. The enhanced antibacterial activity of ABT-492 relative to ciprofloxacin, levofloxacin, and trovafloxacin is likely to be explained, in part, by its potent interactions with bacterial topoisomerases. ABT-492's equivalent activity against both the DNA gyrase and the topoisomerase IV of pathogens, give ABT-492 a potential for decreased development of resistance.

The *in vitro* potency data suggests that ABT-492 has the potential to be therapeutically effective at doses comparable to trovafloxacin and superior to levofloxacin. In addition, ABT-492 was consistently more potent than trovafloxacin against MRSA and vancomycin-resistant enterococci. In both these cases, however, therapeutic utility remains to be assessed in the clinical setting.

S. pneumoniae was chosen as the dose-defining pathogen since it is the key pathogen in severe respiratory tract infections and treatment of infections caused by this pathogen has traditionally been a weakness of most quinolones. For treatment of fluoroquinolone-susceptible *S. pneumoniae* respiratory tract infections, oral dosing may be similar to trovafloxacin based on data generated in lung infection models. Because of the excellent potency of ABT-492 against fluoroquinolone-resistant *S. pneumoniae* with an MIC₉₀ of 0.12 µg/ml, this group of emerging strains may be targeted as a key differentiation point from other quinolones. Also, data from the thigh infection model suggests significantly greater efficacy for ABT-492 than for trovafloxacin.

The Market

ABT-492 is broad-spectrum anti-infective agent with potential application across a broad range of indications, including respiratory infections, genito-urinary infections, and skin/soft tissue infections. It is assumed that a pediatric formulation would not be a part of the primary development plan due to the known adverse events caused by quinolones in pediatric populations. Nonetheless, reports of quinolone pediatric development has been reported (gatifloxacin), hence the pediatric market should be regarded as a potential upside for this quinolone should its safety profile merit its use in pediatrics.

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Current Treatment Options

Class	Mechanism of Action	Comments
Penicillins	Cell wall synthesis inhibitor	Mostly generic, class has seen significant decrease as a result of penicillin resistance.
Cephalosporins	Cell wall synthesis inhibitor	Some generic, class has seen significant decrease in use as a result of prevalence of β -lactamase producing strains and modification of penicillin-binding proteins.
Tetracyclines	Protein synthesis inhibitor	Generic agents, relatively high levels of resistance but are still useful in some indications.
Sulfonamides	Folic acid synthesis	Generic agents, relatively high levels of resistance but are still useful in some indications.
Macrolides	Protein synthesis inhibitor	Widespread use in RTI, macrolide resistance has been increasing rapidly, but has not yet translated into declines in clinical efficacy; <i>H. flu</i> activity continues to be class weakness, along with GI adverse events, drug-drug interactions, & taste perversion.
Quinolones	DNA synthesis inhibitor	Fastest growing antibiotic class, used in a broad spectrum of indications; class historically associated with poor Gram+ pathogen coverage and sub-optimal safety profiles; newer agents (Levaquin, Tequin, Avelox) have improved dramatically along both spectrum and safety dimensions.
Oxazolidinones	Protein synthesis inhibitor	Newest antibiotic class to reach market, due to limited Gram- profile will be used primarily in nosocomial setting.

U.S. Market

1999 U.S. antibiotic prescription and sales data are presented in the table below.

		1995	1996	1997	1998	1999	CAGR ₁₉₉₅₋₉₉	
U.S.	TRXs (MM)	Tab/Cap.	220	215	211	208	221	0.1%
		Oral Susp.	76	66	63	59	61	-5.3%
		I.V.	NA	NA	NA	NA	NA	NA
	Sales (\$MM)	Tab/Cap.	\$4,857	\$4,220	\$4,467	\$4,848	\$5,715	8.9%
		Oral Susp.	\$1,075	\$979	\$977	\$1,001	\$1,120	1.0%
		I.V.	\$1,865	\$1,829	\$1,855	\$1,890	\$2,117	3.2%

Tab/cap and oral suspension prescriptions had been declining 1-2% per year in the period of 1995-1998, presumably from increased attention to appropriate prescribing in the face of increasing resistance; however, prescriptions recovered in 1999, though this may be explained at least in part by a relatively late 1998-99 flu season. Even in the face of this negative pressure on antibiotic use, however, sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics; during 1995-1999, generic tab/cap prescriptions declined by 30MM. So while negative pressure on the use of these antibiotics continues, it appears the market is willing to bear higher costs for agents that meet unmet need. The IV market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

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Quinolones have seen dramatic growth, with oral and IV sales growing at 17% and 16% compound annual rates, respectively, from 1995-1999. This growth is a function of the newer quinolones successfully penetrating the RTI segment, which was initiated with the 1997 launches of Levaquin and Trovan (withdrawn) and continues with the recent introductions of Tequin and Avelox.

Ex-U.S. Market

Ex-U.S. sales of antibiotics totaled \$11.7 billion in 1999. The tab/cap represents the largest segment, with sales of \$9.4 billion on 770 MM TRX. TRX growth has been flat, with a 1995-99 CAGR of 0.5%; the use of antibiotics is predicted to slowly decline due to more judicious use of antibacterials in the face of increasing bacterial resistance.

Ex-US, the quinolone class accounted for 8% (62MM) of total tab/cap market prescriptions and 13% of sales (\$1.2 billion). Ciprofloxacin is the market leader ex-US, with approximately 47% of the quinolone market Rx's (29MM) and 44% (\$530MM) of sales. Levofloxacin launched in many European markets in 1998/1999 and holds approximately 14% Rx share of the European quinolone market, and 0.8% of the overall tab/cap market. Although grepafloxacin and trovafloxacin also launched in some European countries in 1999, both products were recently pulled from the market due to liver toxicity and other complications. Moxifloxacin launched in Germany in Q4 1999, but has not yet been approved in other markets. In Japan, levofloxacin launched in 1994 and still commands a 65% Rx share of the quinolone market and 10% of the Japanese tab/cap market overall. Japan accounts for approximately 80% of ex-US levofloxacin sales (\$370MM).

1999 Ex-US Tab/Cap Market						
Class	Sales (\$MM)	Sales Share	Sales CAGR '96-'99	TRXs (MM)	TRX Share	TRX CAGR '96-'99
Market	\$9,348	-	3.6%	770	-	0.8%
Quinolone Class	\$1,219	13%	-12%	62	8%	NA
Cipro	\$530	53%	4.9%	23	3.8%	NA
Levaquin	\$466	5.0%	NA	18	2.3%	NA
Trovan	\$12	0.1%	NA	0.5	0.1%	NA

Competition

The anti-infective pipeline is very competitive, but most of the competition is focused on improving the activity and safety of the quinolones. Ketolide development is the only other area of activity which is in late stage of development. The quinolone compounds in present development may fall out because of safety or lack of activity against resistant pathogens.

Competitive Analysis - Emerging Competition					
Product	Company	Class	Phase/Estimated Time to Market	Country	Comment
Kensk (telithromycin)	Aventis	Ketolide	Filed 3/00 Est. launch 3/01	U.S.	Respiratory indications; filed NDA 3/00; 800 mg QD; first in ketolide class to reach market.

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Competitive Analysis – Emerging Competition					
Product	Company	Class	Phase/Estimated Time to Market	Country	Comment
Factive (gemifloxacin)	SKB	Quinolone	Filed 12/99 Est. launch 12/00	US	Superior to quinolones for MRSA; highly potent vs. RTI pathogens <i>H. flu</i> , <i>M. cat</i> , and <i>S. pneumo</i> and UTI pathogens <i>E. coli</i> and <i>P. mirabilis</i> ; CRSP; potency > spar, trov, gcpa and ≥ moxi; activity vs. <i>P. aeruginosa</i> ; good atypical and mycoplasma coverage; intracellular penetration; low photo/CNS tox; 700 patient database
Sitafloxacin	Daiichi Sankyo	Quinolone (IV only)	III II Est. launch 2002	Japan U.S., Europe	Very potent MRSA, pseudomonas and bacteroides activity; diarrhea, ALT, low WBC; will likely be target to severe rather than community infections
Eccenofloxacin	Chief Foods	Quinolone	II Est. launch 2002	UK	Active against UTI and RTI pathogens; superior to home and oflo vs. <i>P. aeruginosa</i> . T _{1/2} = 14-19 hr; will likely be target to severe rather than community infections
CS-940	Sankyo	Quinolone	II Est. launch 2002	Japan	Active against G ⁺ /; excellent activity against <i>H. flu</i> , <i>C. jejuni</i> , <i>M. pneumo</i> , and <i>C. trochomatis</i> ; greater potency than cipro; t _{1/2} ~7 hr; BA ~80%
T-3811	Toyama/Eli Lilly	Quinolone	I Est. launch 2005	Japan	Excellent potency and low toxicity
DC-756	Daiichi Pharma	Quinolone	Pre-clin Est. launch 2006	Japan	Low toxicity; in vitro potency ≥ trov, STFX & HSR-903

Unmet Needs

Overall unmet need in the anti-infective market is low. Resistance represents the largest unmet need, which will continue to evolve over time. Satisfaction with other product attributes, such as convenience, spectrum of activity, and tolerability/safety is quite high. Any improvements in these areas will be incremental and will offer little in the way of differentiation.

ABT-492 is one of the most active agents against the resistant organisms. It has indications that will have a low propensity for the development of resistance. ABT-492 will be developed to maximize any opportunities to shorten therapy. ABT-492 was chosen from hundreds of quinolones because of its potential to be well tolerated and safe in humans. ABT-492 will have few interactions with other drugs.

Unmet Need	Pipeline Impact
Activity against resistant organisms	<i>Strep. pneumo</i> , MRSA, and VRE represent most problematic pathogens although new quinolones/ketolides do well with most resistant <i>Strep. pneumo</i> strains; quinolone-resistant <i>Strep. pneumo</i> may develop; pseudomonas resistance is also increasing; resistance will likely continue to be a source of unmet need due to its dynamic nature.
Low propensity for resistance development	Given that most compounds in development are from classes of drugs already in use, this need is largely unmet. Unclear how quickly resistance will build to new classes of drug; gemifloxacin claims 8-methoxy functional group results in lower propensity for resistance development
Convenience (duration/frequency)	Standard moves toward 5-7 days of therapy with QD dosing; may start to see 3-day therapies for some indications (AECB)
Increased tolerability	While some degree of unmet need exists, increasingly, agents (which have not been withdrawn) are reaching the marketplace with adverse event profiles that approach clinical insignificance; a very clean safety

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	profile should be regarded as a necessary component rather than a differentiating one
Few drug-drug interactions	Quinolones, macrolides, and ketolides all interact with other drugs to varying degrees; a potent drug with no interactions would be a benefit in this market

Considerations

Product Usage: Physicians are likely to use ABT-492 for the sicker patients with the most difficult infections to treat. In the outpatient arena it will be used to treat community-acquired pneumonia and acute bacterial exacerbations of chronic bronchitis in the older patients with an underlying illness. It will also be used in the hospital for the community-acquired pneumonia patient who requires hospitalization and for serious nosocomial infections.

While many regard quinolones as agents that should be reserved for 2nd line use, their activity against *H. influenzae* and resistant *Strep. pneumoniae* (which current macrolides do not offer) have resulted in a high level of acceptance for empiric 1st line use. The improved safety profiles of several recent quinolones have facilitated their use as 1st line agents. Provided that ABT-492 is proven to have a benign safety/adverse event profile, it will likely receive usage in both 1st-line (non-severe) and 2nd-line (severe) infections.

Side Effects: The quinolone class has potential prolongation of the QT interval and other cardiovascular effects. There is also increased regulatory scrutiny due to recent quinolone withdrawals from international markets. ABT-492 has been evaluated in the standard *in vivo* models used to evaluate QT interval potentials of other antibiotics and has shown no evidence of increasing QT. Also, compared to marketed quinolones, preclinical studies show no evidence of no increase incidence of CNS drug concentration (ie, less potential for dizziness); phototoxicity; and liver toxicity.

Off-label use: It is difficult to predict at this time what off-label uses will be seen for this compound. Initial development will be for the more common respiratory, urinary tract, skin, and hospital infections. Other indications will be evaluated after the primary approval of this compound. Many of the secondary indications will get usage before we have regulatory approval.

COGS: The initial cost of goods is in \$6000/kg range, but will come down rapidly after the initial starting materials are determined. At time of launch ABT-492 will have a cost of goods in the \$1500/kg range which is competitive compared to other quinolones and other new antibiotics.

Dosing: Based on animal models and the *in vitro* activity of ABT-492 the dose for most oral indications will be in the range of 100 to 200 mg give once daily.

Development/Regulatory: Anti-infective compounds are well understood by regulatory agencies globally and they have clearly defined clinical development path and regulatory guidelines for reference. Abbott Laboratories has been in this arena for many years and has experience with the FDA and European regulatory agencies and so the hurdles to development are well known. ABT-492 has begun but not yet completed its first Phase I study in healthy volunteers.

Other Approaches: Because of the well defined development guidelines there are not many options. The major development options are in dosing regimens. ABT-492 is a very potent drug which has demonstrated rapid killing of pathogens *in vitro* and *in vivo*, and the development plan will attempt to shorten treatment durations to increase the competitive advantages of this activity.

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Pricing: The community infection market is quite competitive from a pricing standpoint, with recent quinolones priced at approximately \$45 per 5-7 days of therapy. The pricing strategy will depend on strengths/weaknesses of the ABT-492 product label, the competitive landscape at launch, and the managed care environment, but current pricing assumption is parity for ABT-492 with respect to other quinolones.

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ABT – 510

Descriptive Memorandum

February 2001

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ABT 510

Overview

There is abundant evidence that primary tumor growth and metastatic progression require new blood vessel formation (angiogenesis). Tumors secrete inducer proteins including bFGF and VEGF that activate microvascular endothelial cells (EC) causing them to proliferate, migrate and organize into capillary structures. Activated endothelial cells also enhance malignant progression by producing signal molecules (cytokines) that inhibit programmed cell death (apoptosis) of tumor cells. Since anti-angiogenic therapy targets genetically stable endothelial cells, resistance typically seen following cytotoxic chemotherapy is not observed. Moreover, angiogenesis inhibitors should not have the intrinsic toxicity of anti-proliferative chemotherapy. Angiogenesis is also a feature of several other pathophysiologic states of large unmet medical need (macular degeneration, psoriasis, and arthritis, among others).

Angiogenesis sustains the growth and progression of tumors. Unlike chemotherapy or radiation, both of which can damage normal cells in addition to tumor cells, anti-angiogenic agents are hypothesized to prevent growth of new blood vessels and to disrupt critical tumor survival signals produced by EC. These agents may keep tumors in a dormant state for as long as the compound is administered and tumor regressions may occur. Proof of this principle has been demonstrated in pre-clinical models. Currently, at least thirteen compounds with anti-angiogenic activity in cancer are in various phases of clinical development, however few act directly and specifically on the angiogenesis process. Anti-angiogenesis drugs are not expected to replace or compete with current therapies. Instead, if these agents prove to be effective, it is believed that they will be used as supplemental therapy to prevent metastasis following surgery, cytotoxic chemotherapy or radiotherapy. As for cases where tumors have already metastasized, these agents could slow down disease progression and maintain "disease dormancy".

Thrombospondin-1 (TSP-1) was the first natural angiogenesis inhibitor to be discovered. TSP-1 is a large, multifunctional protein. TSP-1 rapidly inhibits EC migration and increases EC apoptosis through activation of caspase-3-like proteases. The normal tissue expression of TSP-1 limits inappropriate neovascularization, however it is transcriptionally activated by the tumor suppressor gene product p53. Therefore, TSP-1 is down-regulated and under-produced in p53 defective tumors. In rodent models, ectopic overexpression of TSP-1 inhibits the malignant phenotype as does direct administration of TSP-1 in the circulation. However, direct clinical use of TSP-1 is not feasible because of its scarcity, large size and multiple other biological functions.

The angiogenic activity of TSP-1 has been localized to the 50,000 MW N-terminal stalk region of this protein, and more specifically to the properdin (Type-1) repeats within this region. Although small synthetic peptides within this region have only weak antiangiogenic activity, it was discovered that a single D-amino acid replacement in a properdin region peptide led to an increase in activity of greater than 1000-fold. ABT-510 is a parenterally available nonapeptide. Although ABT-510 competes with TSP-1 for binding to the EC, the exact mechanism of anti-angiogenesis is unknown.

ABT 510 is supplied for clinical use as a sterile solution in acetate salt in 5% dextrose. ABT 510 is soluble and stable in water.

In vitro, ABT 510 inhibits chemotactic VEGF/bFGF-stimulated migration of human microvascular endothelial cells (EC) with an IC50 of approximately 0.250 nM. This effect is EC specific. ABT-510 (10mg/kg/day subcutaneously) blocks VEGF-induced corneal vascularization in mice. It potently and selectively competes with TSP-1, binding the CD 36 receptor.

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ABT 510 inhibits tumor progression *in vivo*. ABT 510 (20mg/kg/day subcutaneous administration) inhibited tumor progression (78% growth inhibition at day 38) in a model of human breast cancer (MDA-MB-435) growing in the breast pads of nude mice. Dose dependent inhibition of B16F10 melanoma lung metastases was observed in a second murine model. ABT 526, a molecule highly similar to ABT 510 (which was not advanced into human trials because of concatamer formation) was administered to 23 companion dogs (25mg SQ BID) with sporadic cancers (head and neck carcinoma, lymphoma, sarcoma, etc) refractory to conventional chemotherapy. Surprisingly, 2 complete responses, 5 partial responses ($\geq 50\%$ shrinkage) and 6 cases of disease stabilization were observed.

Assays for toxicity, histamine release, hemolysis, T-cell function neutrophil migration, platelet aggregation, receptor (CEREP) screening and CNS function were unremarkable. ABT-510 produced no physiologically significant changes in cardiovascular or hemodynamic function in anesthetized dogs. In addition, there were no physiologically significant changes in clinical blood chemistry profiles or cardiac electrophysiologic function in response to ABT-510. Doses that were many times higher than the predicted efficacious concentration produced a moderate reduction in mean arterial blood pressure in conscious monkeys. ABT-510 was not mutagenic in the Ames assay. It is concluded therefore that ABT-510 has an excellent pre-clinical safety profile.

ABT-510 is currently in Phase I clinical trials. Because of its exceptional safety profile, normal volunteers are being dosed with ABT-510 to establish human safety and pharmacokinetic parameters. Review of these data will lead to a Go/NoGo decision for Phase II trials in the Summer of 2001.

The market

Cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market. The market for products to treat cancer is changing rapidly. It is a growing market fueled by:

- Increasing disease incidence
- New product entries
- New therapeutic paradigms
- A growing adjunctive market, which increases the number of patients eligible for chemotherapy
- Intense research and competition

The increase in the aging population in developed countries increases the incidence of cancer. The diagnosed cancer incidence and prevalence in seven major markets, including the U.S., France, Germany, Italy, Spain, U.K. and Japan are close to 3 million and 10 million respectively. The numbers are increasing steadily. Currently, about one-third of the new medicines in development are targeted against cancer.

Cancer is not a single disease, but includes more than 100 different disorders, which have at their core uncontrolled cell growth. Of these disorders, the cancer types that offer the greatest commercial opportunity include breast, colorectal, lung, ovarian and prostate (based on incidence/prevalence/unmet need). Treatment of breast, lung and prostate cancers account for more than 50 percent of the direct medical costs of cancer therapies. Other cancer types, specific to one or more of the major international markets, may provide niche opportunities. For instance, stomach (gastric) cancer is relatively common in Japan but not in the U.S. or Europe; similarly, liver cancer has a greater occurrence in Japan, Italy and Spain.

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JH 008188

Depending on tumor type, cancer can be treated with surgery, radiation, chemotherapy (cytotoxic), hormonal therapy or a combination of any of these. For the purpose of this analysis, we will define the cancer market as chemotherapeutics and the adjunctive therapies used to counter the effects of chemotherapy and radiation therapy. The following charts summarize the global sales for these products.

Global Sales by Market Segment (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	CAGR '96-'98
Hormone	4,414	4,784	4,884	5.2%
Cytotoxic	4,278	5,212	6,268	21.0%
Adjunctive	3,357	3,651	4,166	11.2%
Total	12,059	13,647	15,318	12.7%

Source: Datamonitor

Sales by Region (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	CAGR '96-'98
US	5,564	6,276	7,422	15.5%
Ex-US	6,495	7,370	7,896	10.3%

Source: Datamonitor

Chemotherapeutic agents

Cytotoxic therapies include classes such as alkylating agents, anti-tumor antibiotics, anti-metabolites and antimitotics (taxanes). These agents are toxic and demonstrate dose-limiting side effects. The commercial value of this segment is significantly understated, as most of the products are available in generic form.

The growth of the cytotoxic segment in the past three years has been driven primarily by the introduction of new, more effective and expensive therapies such as Taxol (paclitaxel/BMS), Gemzar (gemcitabine/Lilly), Taxotere (docetaxel/RPR) and Hycamtin (topotecan/SB). Utilization of these newer agents, however, appears to be dependent on the cost sensitivity of the local market. For example, secondary sources indicate that Taxol has recorded over 60% of its global sales in the US market alone and is prescribed with far less frequency in the more cost sensitive UK, German and French markets.

Most chemotherapeutic agents are indicated for just one or two cancer types, but get significant off-label use once approved. Up to 60% of an oncology product's use is potentially for off-label indications. Much of this use is driven by the publication of data and/or approvals in other countries.

Hormonal therapies

Of the top-selling drugs in each major geographical region, *hormone therapies* contribute approximately one-third of the sales ex-US and one-fourth in the US. Hormone therapies for the treatment of cancer include Lupron (leuprolide/TAP), Zoladex (goserelin/Zeneca), Nolvadex (tamoxifen/Zeneca) and other agents used to treat hormone responsive diseases such as prostate and breast cancer. These agents are generally administered chronically and have reduced side effects compared to cytotoxic therapies. Sales of this category are driven primarily by Lupron and Zoladex. The US market has become increasingly cost sensitive in the Medicare sector, which accounts for over 70% of Lupron sales.

Adjunctive agents

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The availability of effective *adjunctive agents* also allows the cytotoxic chemotherapeutic agents to be administered at higher doses and/or more frequently, or used in a more palliative role, since the adjunctive therapies can reduce the impact of the chemotherapy on the patient's quality of life. Agents in this class include immunostimulants, anti-emetics and bisphosphonates. The growth of this market is linked to the growth of the cytotoxic market, as the increased use of cytotoxic agents drives an increased use in adjunctive therapy. The highest selling product in this class is Neupogen (filgrastim/Amgen) with 1998 sales of over \$1 billion.

Biologic Therapy

New therapies under development offer the promise of fulfilling several unmet needs in the treatment of cancer. Experts have predicted that in the future early therapy for breast cancer will be dominated by biological approaches, such as monoclonal antibodies (Herceptin/Genentech), which is widely thought to have strong market potential. Genentech recently reported strong second quarter sales of the product in the US of \$46.2 million, and it is estimated that if only half of US women with breast cancer who over-express this gene received Herceptin, sales would top \$600 million. In addition to monoclonal antibodies, other biological approaches include vaccines and gene therapy.

Future Trends

Emerging science in the past decade offers the potential to radically alter the paradigm for cancer therapy and presents opportunities for fundamentally new ways of approaching the disease. New therapies offer the promise of fulfilling several unmet needs in the treatment of cancer. These include matrix metalloproteinase inhibitors (MMPis), continued expansion of biologics, photodynamic therapies (PDT), anti-angiogenics, and multiple drug resistance (MDR) modifiers. This market does not yet exist, though success of "cytostatic-like" treatments, such as hormonal therapies for prostate and breast cancer, suggests that the market potential for cytostatic agents could be significant.

Competition

The angiogenesis pipeline is very competitive, but this level of intensity is somewhat skewed by the large number of mechanistic approaches that are being claimed to demonstrate angiogenic activity. Furthermore, clear evidence of efficacy for these agents has not yet been demonstrated. For the purposes of this summary, only those compounds considered true anti-angiogenic compounds have been included. Companies with compounds in clinical development include Genentech, Entremed, Sugen, TAP, Magainin and Pharmacia Upjohn.

Angiogenesis Compounds in Clinical Development

Compound	Indications	Company	Phase
Neovastat	Solid tumors	Aeterna	III
RhuMab VEGF	Cancer	Genentech	II/III
Vitaxin	Arthritis, psoriasis, CVR	Ixsys	II
SU-5416	Cancer	Sugen	II/III
TNP 470	Cancer, arthritis	TAP	II
Thalidomide	Cancer	EntreMed/BMS	I
Squalamine, squalus	Cancer	Magainin	I
RPI 4610	Cancer	Ribozyme	I
VEGF antagonist	Cancer, retinopathy	NeXstar	I
Angiostatin/Endostatin	Cancer	EntreMed	I

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JH 008190

Unmet Needs

Cancer remains the second leading cause of death in the United States, Europe and Japan, and consequently, offers an attractive market opportunity for the pharmaceutical and biotechnology industries. This year about 563,100 Americans are expected to die of cancer, more than 1,500 people a day. In the US, 1 or 4 deaths is due to some form of cancer. In 1999, about 1,221,800 new cancer cases are expected to be diagnosed.

For most cancers, the level of physician satisfaction with current therapies is low. It has long been recognized by researchers, physicians, patients and family members that current treatment options may often be as devastating as the underlying disease.

Unmet needs in this market vary by tumor types and stages, with some tumors responding to treatment with better mortality and/or morbidity results than others. However, cancer is still treated as a terminal illness with significant shortcomings in present treatments. In general, unmet needs include:

Need	ABT-510 Attributes
Enhanced efficacy of therapeutic agents	Potential for enhanced efficacy
Reduced toxicity	Potential for reduced toxicity over current cytotoxic treatment
Improvements in drug administration	TBD
Improved target delivery of cytotoxics and novel therapeutics	Unknown
Proven outcomes data	Quality of Life and Pharmacoeconomics to be assessed

Considerations

Product Usage: Physicians have indicated that they would use anti-angiogenic agents initially in their more refractory patients, as follow-on or add-on to current best therapy (chemo or surgical). With experience and clinical evidence, they would be willing to use these agents in earlier stages of the disease, where they perceived the greatest benefit to be. Anti-angiogenesis agents are regarded as a maintenance therapy to be used in early disease or after primary therapy as a prophylactic process to prevent the spread of malignancy. Of course, their ultimate use will depend on the benefit provided, which cannot be determined until clinical trials have been completed. Efficacy evidence in humans manifested by tumor response of the magnitude seen in the preliminary dog studies would stimulate tremendous enthusiasm in the oncology community.

Product Benefits/Efficacy: Physicians are looking for improvements in time to tumor progression and prevention of metastases with cytostatic agents. There is a great deal of enthusiasm for this mechanism in the scientific and lay audience. The concept is very intuitive. Products, such as ABT-510, that promise a clinical benefit without the usual toxic trade-offs associated with current chemotherapeutic agents, will be enthusiastically received by oncologists.

Side Effects The proposed safety profile of anti-angiogenic agents may enhance usage, as the dose limiting toxicity profiles of most of the other available agents has established a much lower hurdle for demonstrating a preferred profile. However, as chronic therapy, anti-angiogenic agents may have to demonstrate a cleaner profile than cytotoxic agents do to ensure compliance.

Off-label use: Off label use accounts for between 30-60% of an oncology product's usage. Off-label use is driven by publication of clinical trial results in credible journals, listing in key compendia and/or a peer's experience with the product. Therefore, development spend for off-label use is considerably less than the spend required for regulatory approval of an indication. However, promotion of these off-label uses is limited.

Other indications: ABT-510 may be effective in other therapeutic roles, such as arthritic diseases and macular degeneration. These other indications may offer a commercial upside, through internal development or co-development/out-licensing opportunities.

Competition: While there are a relatively large number of angiogenesis inhibitors in development, it is unclear whether they will demonstrate a superior efficacy or side-effect profile vs. ABT-510. The mechanism of angiogenesis suggests that multiple anti-angiogenic approaches may be required to maximize the clinical benefit.

COGS: Initial estimates on finished cost of drug place it in the range of Lupron costs. Depending on final dosing requirements, the cost of this compound could become a significant obstacle. However, this will need to be considered in light of the pricing flexibility in the oncology market, where there is limited pricing sensitivity for products that are reimbursed. Any financial analysis will need to include royalty obligations to Northwestern University.

Dosing: There is still some uncertainty regarding the route of administration and feasible dosage forms for ABT-510. An "inconvenient" formulation leaves this product extremely vulnerable to competitors with more convenient dosage forms. A convenient dosage form, such as a monthly depot, will enhance product adoption over a less convenient form. However, the effect of the various dosage forms on product adoption will be dependent on the benefits the compound provides, side-effect profile and availability of competitive agents with more convenient dosage forms. For chronic therapy, convenience will play an important role in market penetration, given alternative agents. Although less convenient than oral therapy, parenteral therapy (depot, but not self-administered sub-cutaneous) is currently reimbursed by Medicare in the US. Over 60% of all cancer patients have Medicare as their primary healthcare coverage in the US.

Development/Regulatory: With a new class of compounds, there is not a clearly defined clinical development path or regulatory guidelines for reference. This hurdle is similar for all the competitive products, but increases the overall development risk profile for these agents. However, with several anti-angiogenic agents in late stage development, Abbott can learn from their experience.

Other Approaches: Other "cytostatic" approaches may present a competitive threat if they are used as substitutes. Due to the complexity of the pathogenesis of cancer, it is more likely that these agents will be used in combinations, but incremental benefits may become more difficult to demonstrate as the number of products and approaches multiply. This will require additional studies, as these other classes become part of standard cancer treatment. However, this threat is not unique to this compound.

Pricing: The treatment of cancer is expensive, so there is the potential for a great deal of pricing flexibility in this market. There is also an increasing emphasis on cost-effectiveness studies that will need to be addressed in the development plan.

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ABT - 518

Descriptive Memorandum

February 2001

Abbott Laboratories

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MMPi

Overview

Abbott's Matrix Metalloproteinase Inhibitor (MMPi) program represents a novel therapeutic class, with the potential to alter the way that cancer is treated by preventing or modifying disease progression and/or metastases. This more "chronic" approach to therapy has the potential to transform cancer into a disease that patients live with, much like the effect of HIV protease inhibitors on patients with AIDS. It also has the potential to expand the cancer market significantly by increasing the average length of treatment and expanding the pool of patients eligible to receive therapy.

The MMPs comprise a family of enzymes that degrade a wide range of matrix protein substrates. High expression of these enzymes occurs in cancer and is associated with the ability of tumors to grow, invade, develop new blood vessels and metastasize.

MMP inhibitors (MMPis) may suppress the progression of tumors by several mechanisms:

- Suppress invasion/metastasis by blocking the membrane traversal and access to blood/lymphatic vessels
- Blocking the remodeling of extra-cellular matrix in the vicinity of primary tumors to prevent stroma-bound growth factors from stimulating tumor growth
- Blocking angiogenesis by preventing the proliferation and migration of endothelial cells and neovascularization of tumor.

Experimental evidence suggests that gelatinase A and gelatinase B are particularly important in tumor progression, consequently the project team has targeted gelatinase selective inhibitors for the treatment of cancer. Another reason for targeting highly gelatinase-selective MMP inhibitors relates to the side effect profile exhibited by broad-spectrum agents like marimastat. Chronic administration of marimastat causes a dose-limiting side-effect characterized by severe joint pain and stiffness. Since these joint effects may be mediated by inhibition of other MMPs like fibroblast collagenase, highly gelatinase selective agents may be efficacious without producing dose-limiting side effects.

The MMP selectivity profile exhibited by ABT-518 distinguishes it from competitor's compounds. ABT-518 possesses sub-nanomolar inhibition potencies versus both gelatinase A and gelatinase B and is substantially more selective for the inhibition of the gelatinases over fibroblast collagenase than marimastat and prinomastat. Despite its high selectivity, ABT-518 demonstrates antitumor activity equal or superior to prinomastat. Inhibition of tumor growth is dose dependent in both syngeneic and xenograft models. ABT-518 is also effective in blocking vessel formation in a mouse model of angiogenesis. ABT-518 is a stable crystalline solid which can be synthesized in six steps (25% overall yield) from commercial starting material.

ABT-518 gives rise to sustained plasma concentrations following single oral dosing in monkeys, dogs and rats. Bioavailabilities range between 68 and 93% depending on formulation and species. Several metabolites are produced after repeated oral dosing of ABT-518, although their relative amounts varies with gender and species.

ABT-518 displays no meaningful effects in genotoxicity, cytotoxicity and ligand binding assays and its cardiovascular effects in dogs are unremarkable. ABT-518 produces no significant toxic effects in rats treated with 100 mg/kg/day over 28 days. Plasma concentrations generated by ABT-518 in these studies are at least 20-fold higher than those necessary to produce efficacy in cancer animal models. ABT-518 is therefore a compelling development candidate with the potential to

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JH 008194

demonstrate antitumor effects superior to the MMP inhibitors currently undergoing clinical trials. Phase 1 clinical trials in cancer patients began March 2001.

The market

Currently, cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market.

Global Sales by Market Segment (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
Hormone	4,414	4,784	4,884	5,000	5.2%
Cytotoxic	4,278	5,212	6,268	7,300	21.0%
Adjunctive	3,367	3,651	4,166	4,900	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

Sales by Region (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex- US	6,495	7,370	7,896	8,700	10.3%

Source: Datamonitor

Cytostatic agents have the potential to alter the way cancer is treated and presents opportunities for fundamentally new ways of approaching the disease. This cytostatic market does not yet exist, though success of more cytostatic "like" treatments, such as hormonal therapies for prostate and breast cancer, suggest that the market potential for cytostatic agents could be significant.

The ultimate commercial and clinical success of the MMPi will depend on the clinical benefit this product provides in key cancer types compared with current best therapy. These can be benefits provided by dosing this agent in addition to current therapy and/or as an alternative to best therapy, or as a new component of best therapy. All currently available products, including the market leaders such as Taxol, have significant shortcomings in their profiles.

However, as novel therapy, MMPi's will probably be adopted initially as add-on the current chemotherapy. As benefits are proven and clinical experience is gained, these agents may be used in earlier stages of cancer and/or in conjunction with surgery or radiation to prevent the progression of any microscopic disease that remains.

The clinical targets identified for this compound include late stage pancreatic cancer, late stage NSCL cancer (on-label), with late stage ovarian and breast cancer as additional cancer types where efficacy has been demonstrated, but not filed. Other cancer types this compound may be efficacious in include SCL, colorectal, bladder, stomach and prostate. Targets will be refined as we know more about this compound's in-vivo activity.

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JH 008195

The following tables summarize the key marketed competitive products by indication (US data only):

Late Stage Breast	
Product	Share
Cyclophosphamide/Cytoxan/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	16.25
Paclitaxel/Taxol/BMS	16.11
Trastuzumab/Herceptin/Genetech	11.26

Late Stage NSCL	
Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

Late Stage Ovarian	
Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/Alza	9.14
Cisplatin/Platinol/BMS	7.58

Late Stage Pancreas	
Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Efudex/ICN Pharma	21.0
Leucovorin/	10.7
Cisplatin/Platinol/BMS	4.72

Compounds in Development

The MMP inhibitor field is competitive. More than 30 firms have filed patents claiming small molecule MMP inhibitors over the past 5 years, and several companies have compounds in advanced clinical development. Abbott's compound may be 3rd or 4th to market and will have to demonstrate a competitive advantage to gain the share necessary to support the clinical development of this compound. Companies with compounds in advanced clinical development for the treatment of cancer include Agouron/Warner Lambert/Pfizer, British Biotechnology/Schering Plough and BMS and are listed below. Other companies are targeting this mechanism for arthritis.

MMPs in Clinical Development for Cancer

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Compound	Company	Comments	Phase
Marimistat	British Biotechnology/ Schering Plough	Broad spectrum, dose limiting toxicity. Activity seen in gastric cancer, but negative results in pancreatic.	III
Prinomastat	Agouron/ Warner Lambert/ Pfizer	Moderate gelatinase selectivity, dose limiting toxicity. May be dosing sub-optimally to avoid toxicity. Efficacy data not available.	III
BMS 275291	BMS	Broad spectrum, joint effects seen in Phase I studies.	II

Bayer recently dropped development of BAY 12-9566 due to concerns about potential toxicity. Recent results from a study with marimistat in pancreatic cancer, where adding marimistat to Gemzar resulted in no survival advantage, has led to speculation that MMPis may be more applicable in less aggressive cancer types or earlier stages of the disease. Alternatively, it could be a reflection of the inability to examine higher doses of marimastat due to joint effects.

The joint effects produced by the compounds listed above almost certainly preclude their long-term use, limit compliance and reduce optimal efficacy. Any MMP inhibitor that lacks these side effects will possess a substantial competitive advantage. The musculoskeletal effect produced by marimastat and prinomastat in cancer patients is typically described as arthralgia, myalgia and tendinitis, which occurs predominately in the upper limbs. While mild cases respond to analgesics, interrupting therapy for a period of approximately 2 weeks is necessary when the condition is less well tolerated.

Although Abbott's timing to market is not optimal, the shortcomings of the competitive products provide an opportunity for a compound with an improved SE or efficacy profile. Current animal models seem to predict Abbott's compound is superior to those currently in clinical trials, and has the potential to be best in class.

Product profile

The objective of a product profile at this time in the product's development is to provide a target for the types of attributes that will be required to be commercially successful. This profile is based on market research with oncologists and consultation with opinion leaders. This profile will continue to be refined as more is known about this product's profile, development of competitive products and the market continues to evolve.

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	Base	Optimal
Efficacy	ABT-518, alone or in combination with best therapy, provides at least one of	Provides more than one of the efficacy benefits outlined.

	the following benefits in at least one solid tumor type: <ul style="list-style-type: none"> Increased survival Tumor regression Improved quality of life Increased time to tumor/disease progression 	
Competitive advantage	ABT-518 will need to demonstrate a clinically significant advantage in efficacy (see parameters above) or additive synergistic activity with current/competitive agents or clinically significant advantage in side-effect profile relative to other MMPi agents.	Same
Administration	Convenient administration relative to competitive agents.	Same plus reimbursement in US market.
COGS	A finished cost of goods that is consistent with at least an 80% standard manufacturing margin.	A finished cost of goods that is consistent with at least a 80% standard manufacturing margin.

Marketing overview

Product Usage: Physicians have indicated that they would use MMPis initially in their more refractory patients, as follow-on or add-on to current best therapy (chemo or surgical). With experience and clinical evidence, they would be willing to use these agents in earlier stages of the disease, where they perceived the greatest benefit to be. The MMPi was regarded as a maintenance therapy to be used in early disease or after primary therapy as a prophylactic process to prevent the spread of malignancy.

Product Benefits/Efficacy: Physicians are looking for improvements in time to tumor progression and prevention of metastases with cytostatic agents. The MMPi mechanism has more recently been implicated as having an even more active role in cancer pathogenesis, from preventing primary tumor growth to anti-angiogenic properties. Positive results from competitive agents, such as marimistat in gastric cancer, provides proof of principle for this mechanism.

Side Effects: The proposed safety profile of MMPis (excluding joint toxicity) may enhance usage, as the dose limiting toxicity profiles of most of the other available agents has established a much lower hurdle for demonstrating a preferred profile. However, as chronic therapy, MMPis may have to demonstrate a cleaner profile than cytotoxic agents do to ensure compliance. As the 3rd or 4th MMPi to market, SE hurdles will be even higher for this compound. As a critical Go/No Go decision point, the joint toxicity of this compound will be evaluated in an expanded Phase I multi-dose study.

Dosing: Discovery is currently targeting an oral dosage form. In general, oral therapies are acknowledged by physicians and patients as being more convenient to the patient. Chronic oral dosing may also reduce overall costs, as infusion support products and personnel would not be required, enhancing pharmacoeconomic evidence.

COGS: Initial estimates on finished cost of drug suggest that drug costs will not be significant for this compound

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Off-label use: Off label use accounts for between 30-60% of an oncology product's usage. Off-label use is driven by publication of clinical trial results in credible journals, listing in key compendia and/or a peer's experience with the product. Therefore, development spend for off-label use is considerably less than the spend required for regulatory approval of an indication. However, promotion of these off-label uses is limited.

Competition: As the 3rd or 4th MMPi to market, Abbott's compound will need to demonstrate a meaningful clinical advantage over compounds that are in more advanced development. Strict Go/No Go criteria will determine if the MMPi can meet these hurdles. If they cannot be met, the compound will not move forward.

Development/Regulatory: With a new class of compounds, there is not a clearly defined clinical development path or regulatory guidelines for reference. This hurdle is similar for all the competitive products, but increases the overall development risk profile for these agents. However, with several MMPis in late stage development, Abbott can learn from their experience.

Other Approaches: Other "cytostatic" approaches may present a competitive threat if they are used as substitutes. Due to the complexity of the pathogenesis of cancer, it is more likely that these agents will be used in combinations, but incremental benefits may become more difficult to demonstrate as the number of products and approaches multiply. This will require additional studies, as these other classes become part of standard cancer treatment. However, this threat is not unique to this compound.

Pricing: The treatment of cancer is expensive, so there is the potential for a great deal of pricing flexibility in this market. However, as an oral therapy in the US market, there may be additional downward price pressure for this agent. There is also an increasing emphasis on cost-effectiveness studies that will need to be addressed in the development plan.

Dosing: Discovery is currently targeting an oral dosage form. In general, oral therapies are preferred by physicians and patients because of the convenience to the patient. However, this form may not be the best choice for some people who already have certain digestive system symptoms (vomiting, diarrhea, or severe nausea), cannot swallow liquids or pills, or cannot remember when or how many pills to take. Additionally, in the US market there are several unique factors that currently do not favor oral therapies. Novel oral therapies are not currently reimbursed by Medicare, a significant payer for the oncology patient population. Also, 40-60% of a community oncologist's income is generated through the administration of IV drugs. An oral therapy would not be a source of revenue to the physician.

Clinical Studies

Clinical studies across a wide range of solid tumors will be initiated, including but not limited to breast cancer, non small cell lung cancer, ovarian cancer, pancreatic cancer, etc...

Final indications pursued will depend from the results of the phase II studies.

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JH 008199

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Farnesyltransferase Inhibitor

Descriptive Memorandum

February 2001

Abbott Laboratories

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JH 008200

Overview

The Ras genes were the first oncogenes of mammalian origin to be discovered. Intensive research over the last decade has led to the elucidation of the normal function of cellular Ras protein, the role of Ras mutations in oncogenic transformation, and the identification of molecular targets, such as the enzyme farnesyltransferase, for inhibiting Ras activity. Although farnesyltransferase inhibitors (FTIs) were initially designed with the intention of inhibiting the posttranslational prenylation, and hence function, of Ras, it is now becoming apparent that farnesylated proteins other than Ras (e.g., RhoB) are also critical for malignant growth and may be the relevant target for inhibition of farnesylation. While it remains controversial whether blocking Ras activity or altering the RhoB prenylation status is the actual function of an FTI, these agents, exemplified by ABT-839 and FTIs in the clinic, exhibit remarkable anticancer activity against a wide variety of tumors in preclinical models. The current FTI program is projected to reach DDC status in January, 2001.

Abbott evaluated one FTI, ABT-839, in normal volunteers, but decided to discontinue development of this drug due to its poor pharmacokinetic profile. Invaluable experience was gained, however, from both the preclinical and clinical studies with this compound. Abbott's second-generation series are novel structures that exhibit significantly improved potency and oral bioavailability.

There continues to be tremendous enthusiasm in the medical community and pharmaceutical industry for this mechanism of action. Farnesyltransferase inhibitors have demonstrated impressive antitumor activity in preclinical models with activity equivalent to or better than that achieved with conventional cytotoxic chemotherapy given at the maximal tolerated dose. These agents appear to inhibit angiogenesis and, consistent with this activity, minimal resistance has been observed in preclinical models. The potential also exists for synergistic activity in combination with cytotoxic chemotherapy.

The market

Cancer remains the second leading cause of death in the US, and consequently is an attractive market opportunity for the pharmaceutical/biotechnology industries. Approximately 40% of all Americans will develop cancer in their lifetime.

The worldwide cytotoxic and hormonal cancer therapies market is highly fragmented with only BMS and Zeneca holding a greater than 10% market share. Although the market is not concentrated, the field is highly competitive with more than 60 companies focused on the cancer research area. The growth of the oncology market is fueled by increasing disease incidence, new product entries, new therapeutic approaches, a growing adjunct therapy market that expands the number of patients eligible for chemotherapy, and intensified research competition. The data in Tables 1 and 2 summarize the value of the current oncology market. A great deal of uncertainty surrounds the concept of cytostatic treatment of cancer. Conceptually it may transform the way cancer is treated, allowing patients longer disease free survival and improved quality of life. However, at this point in development, this paradigm does not exist in cancer. Considering market, clinical and patient dynamics factors, breast, colorectal, prostate and non-small cell lung cancers are the most attractive targets for development.

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Table 1. Global sales by market segment (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est.)	CAGR '96-'98
Hormone	4,414	4,784	4,804	5,000	5.2%
Cytotoxic	4,278	5,212	6,268	7,300	21.0%
Adjunctive	3,367	3,651	4,165	4,900	11.2%
Total	12,059	13,647	15,318	17,200	12.7%

Source: Datamonitor

Table 2. Sales by region (\$ MM)

	1996 Sales	1997 Sales	1998 Sales	1999 Sales (est.)	CAGR '96-'98
US	5,564	6,276	7,422	8,500	15.5%
Ex-US	6,495	7,370	7,896	8,700	10.3%

Source: Datamonitor

Cytostatic agents have the potential to alter the way cancer is treated and presents opportunities for fundamentally new ways of approaching the disease. This cytostatic market does not yet exist, though success of more cytostatic "like" treatments, such as hormonal therapies for prostate and breast cancer, suggest that the market potential for cytostatic agents could be significant.

The ultimate commercial and clinical success of the FTI will depend on the clinical benefit this product provides in key cancer types compared with current best therapy. These can be benefits provided by dosing this agent in addition to current therapy and/or as an alternative to best therapy, or as a new component of best therapy. All currently available products, including the market leaders such as Taxol, have significant shortcomings in their profiles.

However, as novel therapy, FTIs will probably be adopted initially as add-ons to current chemotherapy. As benefits are proven and clinical experience is gained, these agents may be used in earlier stages of cancer and/or in conjunction with surgery or radiation to prevent the progression of any microscopic disease that remains.

The clinical targets identified for this compound include late stage pancreatic cancer, late stage NSCL cancer (on-label), with late stage ovarian and breast cancer as additional cancer types where efficacy has been demonstrated, but not filed. Other cancer types this compound may be efficacious in include SCL, colorectal, bladder, stomach and prostate. Targets will be refined as we know more about this compound's in-vivo activity.

The following tables summarize the key marketed competitive products by indication (US data only):

Late Stage Breast	
Product	Share
Cyclophosphamide/Cytosan/BMS	18.7
Doxorubicin/Adriamycin/P&U	17.11
Docetaxel/Taxotere/RPR	16.25
Paclitaxel/Taxol/BMS	16.11
Trastuzumab/Herceptin/Genetech	11.26

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Late Stage NSCL

Product	Share
Carboplatin/Paraplatin/BMS	50.32
Paclitaxel/Taxol/BMS	44.14
Vinorelbine/Navelbine/Glaxo	22.78
Gemcitabine/Gemzar/Lilly	22.14
Cisplatin/Platinol/BMS	11.28

Late Stage Ovarian

Product	Share
Paclitaxel/Taxol/BMS	47.11
Carboplatin/Paraplatin/BMS	45.42
Topotecan/Hycamtin/SKB	22.54
Dox SL/Doxil/Alza	9.14
Cisplatin/Platinol/BMS	7.58

Late Stage Pancreas

Product	Share
Gemcitabine/Gemzar/Lilly	78.5
5-FU/Efudex/CN Pharma	21.0
Leucovorin	10.7
Cisplatin/Platinol/BMS	4.72

Emerging science within the past decade has radically altered the paradigm for cancer therapy and presents opportunities for fundamentally new ways of approaching the disease. Abbott has multiple discovery cytostatic targets, which may improve effective, but we are not alone: more than 200 compounds from other players are in development. The goal of cytostatic therapy is to improve quality of life, controlling the disease and transforming aggressive treatment to a chronic condition, which has been compared to the impact of protease inhibitors on the course of HIV.

Clinical Studies

Considering all the factors, market, clinical and patient dynamics, breast, colorectal, prostate and non-small cell lung cancer appear to be the most attractive targets for development. The development of cytostatic agents faces a number of challenges as regulatory agencies and physicians evaluate the new emerging paradigm of cancer therapy.

Despite the enormous medical need, drugs for chronic treatment/disease stabilization and improved quality of life for cancer patients do not yet exist. Correspondingly, animal models test efficacy that has not yet been validated as predictive of response in humans. Medical oncologists have historically depended on determination of maximum tolerated dose and response manifested by tumor shrinkage for cancer drug development. These parameters are not relevant to novel "cytostatic" agents. Combination with conventional cytotoxic drugs will be required in the near term and will have to be determined empirically. Intermediate and surrogate measures of biological response will have to be developed. Regulatory agencies are grappling with the same issues.

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Competition:Within Project Approach

Company	Compound	Indication	Status of compound	Status of project
Janssen Pharmaceutica	R-11577 (A-251076)	Cancer (unspecified)	Phase III	active
Schering-Plough	Sch66336 (A-265622)	Cancer (unspecified)	Phase II	active
Merck	L-778123	Cancer (unspecified)	Phase I (IV) abandoned	unknown
Bristol-Myers Squibb	BMS-214662	Cancer (unspecified)	Phase I	active
LG Chemical	LB 42908	Cancer (unspecified)	preclinical	active
Roche-Poulenc Rorer	quinuclidine derivatives	Cancer (unspecified)	preclinical	active
Pfizer	unknown structure	Cancer (unspecified)	preclinical	active
Parke-Davis	unknown structure	Cancer (unspecified)	preclinical	active
Roche	peptidomimetics	Cancer (unspecified)	preclinical	abandoned project
Glaxo	peptidomimetics	Cancer (unspecified)	preclinical	abandoned project
Banyu	FPP mimetic	Cancer (unspecified)	preclinical	unknown
ISIS	ISIS-2503 (ras antisense)	Cancer (unspecified)	Phase I	active

Within Therapeutic Area

Approach	Selected Compounds	Company(ies)	Status
antisense	ISIS 3521, ISIS 5132	ISIS	phase I
cytotoxic agents	camptothecin, CI-980, Ixabepron, Genazet, Hycamtin, Irinotecan, Hoxantrone, Oncasine, Capecitabine, Tomudex	Pfizer, Warner-Lambert, Schering, Lilly, SKB, P&U, Immunex, Allcel, Roche, Zeneca	most phase III
differentiation	taqretin, paclitaxel, 5-azacytidine	Ligand, NCI	Ligand in phase III/II
drug resistance modifiers	VX-710, 776C85, RMP-7, CT-2584	Vertex, Glaxo Wellcome, Alkermes, Cell Therapeutics	Vertex in phase II
gene therapy	Onyx-015, MDR1, GLI-328, IL-2, GV-1301	Onyx, Introgen, Therion Biologics, Theragen, Genetic Therapy, Cyclacel, RPR Genetec, GeneMedicine, Tian, etc	Restricted to accessible cancers. Most advanced: Phase III
hormonal therapy	Zolodex, amide, droloxifen, Oncolor, Ruvizor, Casodex, rogletinide	Zeneca, Pfizer, Novartis, Janssen, US bioScience	most phase III
immunotherapy			
antibodies	IDEC-Y2A2B8, anti-HER2, anti-EGFR	IDEC, Genetech, ImClone	IDEC recently approved, others phase III
cytokines	IL-12, IL-4, Proteinkin, Releoron-A	Roche, Schering, Chiron, Roche	phase III
vaccines	NY-ep109, Genevax, MSV	Apollo, Therion, Progenics	phase I, II
photodynamic	phthalocyanine, promycin	CLT photo, Vion	phase II
radiation sensitizers	Neu-Sensamide, radimyl	Oxigene, Roberts	phase II, III
metalloproteinase inhibitors	marimastat AG-3340, CBS-27023A	British Biotech, Apotrin, Novartis, Bayer	BBT in phase III
angiogenesis inhibitors	TNP-470, SU-5416, anti VEGF-mAb, thalidomide, DC101	TAP, Sugen, Genetech, Entemed, ImClone, etc	see angiogenesis project review for details

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Competitive Analysis

The project is on par with others in the industry. While second generation Abbott compounds are not yet in clinic, all of the compounds from other companies that are in clinical trials have deficiencies. While the Schering compound has the best oral PK profile, it is not particularly potent. The Janssen compound is potent, but has a poor PK profile. The Merck compound exhibited QTc prolongation and development has been stopped. The Bristol Myers Squibb compound, BMS-214662, which is in phase I, is an *in vitro* submicromolar inducer of apoptosis in human tumor cells and appears to be the most potent inducer of apoptosis of the known FTIs. This compound could have a different mechanism of action from the classical FTIs and have its own liabilities. LG42908 from LG Chemical is potent FTI and has good oral bioavailability (F=91% in monkey), however, it's a CYP3A4 inhibitor and will have significant drug-drug interaction liabilities. Extensive preclinical pharmacology at Abbott has defined optimum parameters for a FTase inhibitor that may not be known to our competitors, or be achievable with the current generation of FTIs. Although not yet established, we anticipate that the Abbott compound will be improved over competitors' compounds with respect to potency, oral bioavailability, half-life, toxicity, efficacy, angiogenesis inhibition, and lack of resistance.

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DOPAMINE RECEPTOR AGONIST PROGRAM

Descriptive Memorandum

February 2001

Abbott Laboratories

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JH 008206

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D4 Agonists for Male Erectile Dysfunction

Scientific Overview

Male erectile dysfunction (MED) is defined as the "inability to maintain an erection sufficient for satisfactory sexual intercourse" (NIH Consensus Panel) and results from physiological (organic), psychogenic causes, or a combination thereof. This disorder is associated with decreased quality of life, including personal well being, and diminished family and social relationships. In 1999, an estimated 77 million men over the age of 40 (52% of men over 40 years-old) in the seven major pharmaceutical markets experienced some degree of MED, and the prevalence increases with age. Approximately 10-20% of patients have severe or complete MED, and the majority of the population suffers from moderate disease. While the introduction of Viagra has increased the diagnosis rate of MED in the U.S., 75% or more of patients do not seek treatment. However, as the "baby boomer" generation ages, MED will become a more prominent concern and a growing number of patients are likely to seek treatment.

Abbott's male erectile dysfunction program targeting D4 dopamine receptors represents a novel therapeutic approach to the rapidly growing male erectile dysfunction (MED) market. The current gold standard for the treatment of MED, Viagra, acts peripherally at the penile smooth muscle level to induce erection by modulating the levels of cGMP. In contrast, a selective D4 dopamine agonist will act in the brain at the sites necessary for initiation of a successful erection. Targeting the D4 receptors in brain offers the potential for efficacy in patients with MED that do not respond to Viagra (for example patients with diabetes). Additionally, targeting D4 receptors should not result in any cardiovascular adverse events unlike Viagra which can cause serious cardiovascular effects in patients who are on nitroglycerine-based medications. Since safety is of paramount importance for any life-style disorder like MED, a new agent that does not have any contraindications or warnings related to safety issues may be positioned to become the gold-standard therapy.

Evidence for the potential of a selective D4 dopamine receptor agonist for the treatment of erectile dysfunction includes:

- The non-selective dopamine receptor agonist apomorphine (UprimaTM) has been shown to be effective in phase III clinical trials, and has received scientific approval for market in the EU, for the treatment of MED. This validates the utility of dopaminergic agonists to facilitate penile erections in humans. However, the clinical development of apomorphine for the US market has been hampered by dose limiting side-effects (emesis and syncope).
- Studies at Abbott have established that the efficacy of apomorphine (penile erection) and side-effect (emesis) are mediated by different dopamine receptor subtypes. There are 5 known dopamine receptors. Abbott scientists have discovered that the selective activation of D₁ receptors can facilitate penile erection in animals, while the D₂ receptor appears to mediate the emetic effect of apomorphine. The discovery of a D₄ selective agonist maximizes the possibility to identify a compound with equivalent/superior efficacy to apomorphine but devoid of its side-effect liabilities.

PPD is currently screening the Abbott library of compounds to identify novel and proprietary D4 dopamine receptor compounds. Initial hits have been identified that are as potent as any known D4 dopamine receptor agonist. The strategy is to aggressively profile these hits for selectivity across the five different dopamine receptor subtypes and to ensure that selective agents are effective in a number of preclinical in vivo models of MED and have no emetic or cardiovascular side effects. The D4 dopamine receptor agonist program will be discontinued if selective D4 agonists do not achieve at least a 30-fold separation between efficacy in a model of MED and cardiovascular/emetic side effects.

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Abbott has a competitive advantage in the race to exploit selective D4 dopamine receptor agonists for MED. A patent application covering the use of any selective D4 agonist for the treatment of MED has been filed and no other pharmaceutical company may have the range of preclinical models of efficacy and safety in addition to access to the clinical information gained from the development of apomorphine. Our molecular modeling group has facilitated advances in the design of selective D4 agonists.

Market Analysis

The introduction of Viagra combined with increased disease awareness resulted in the MED market in the US exploding from \$157MM in 1997 to an estimated \$726MM in 2000. Worldwide, this market has seen similar growth, and is estimated at \$500MM for ex-US for 2000. Viagra currently dominates the MED market, with more than \$1 billion in sales in the \$1.3 billion worldwide market in 1999, and >95% of the MED prescriptions in the US. The market growth is expected to continue, with an estimated CAGR in the US of 17.9% (2000 – 2005), fueled by increased awareness of MED, expanded use to wider patient segments for relationship or performance enhancement, and the introduction of heavily promoted new agents. Downward pressure on growth will come from continued perceptions of safety concerns, the limited efficacy of ViagraTM, and out-of-pocket cost to patients.

Market drivers influencing the potential of a D4 dopamine receptor agonist include:

- Patient Awareness and Demand Viagra has built considerable awareness of MED. However, in the US, only 10-25% of current MED patients seek treatment for this disorder. Ex-US the percentage of patients seeking treatment is lower (10%). This is mainly due to the lack of DTC promotional campaigns in the ex-US markets. Further market expansion requires continued patient and physician education.
- Product Safety There are growing patient and regulatory concerns regarding the safety of Viagra. While, physicians currently perceive ViagraTM to be safe, if used by the correct patients, there is significant concern regarding the concomitant use of nitrates for cardiovascular disorders with Viagra. Approximately 10% of Viagra patient deaths have been attributed to use of nitrates. Thus, there is an opportunity to eliminate this concern for physicians and to expand the market.
- Product Efficacy In clinical trials Viagra allowed successful intercourse in about 50% of attempts. The limited and inconsistent efficacy of the product has resulted in patient dissatisfaction and discontinuation, thus creating a chance to drive Viagra quitters or switchers, as well as new patients, to new, more effective, MED products. The demonstration of efficacy in a broader population of MED patients might also influence physicians to try an alternative product prior to Viagra. The delay in onset (~1hr) and the variability in onset of action from patient to patient is an additional complaint about Viagra. Product features of a selective D4 agonist such as a more rapid onset of action or more reproducible onset will have a positive influence on the market opportunity for MED therapies.
- Additional Indications Use of a D4 dopamine receptor agon in other indications such as "relationship enhancement" (female sexual dysfunction and age-related decline in male sexual performance) offers an opportunity to both expand the potential market to include women and non-MED sufferers, and reduce the embarrassment of MED for patients. Additional research is required to identify meaningful endpoints in this expanded indication. Initial studies conducted by Pfizer showed that ViagraTM was not effective to treat female sexual dysfunction.

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Competitive Overview

The following tables summarize the key competitive activities in regard to marketed products and products in the development pipeline. To date there are no reports any other company targeting selective D4 agonists for the treatment of MED, although a number of companies do have activities in the dopamine receptor arena for other indications that could be re-focused to MED if they became aware of Abbott's insights into the D4 receptor.

A. Oral agents

Approach	Compound/Product	Company(ies)	Status
PDE5 inhibition	Sildenafil (Viagra TM)	Pfizer	Marketed
DA receptor	Apomorphine (Uprima TM)	TAP	NDA filing withdrawn
Adrenergic	Phenolamine (Vasomax TM)	Schering-Plough/Zenagen	NDA filing on hold (>1 year)
PDE5 inhibition	IC351 (Cialis TM)	ICOS-Lilly	Phase III
PDE5 inhibition	Vardenafil	Bayer	Phase II-III

B. Intranasal

Approach	Compound/Product	Company(ies)	Status
DA receptor	Nasal apomorphine	Nastech	Phase II

C. Intracavernosal agents

Approach	Compound/Product	Company(ies)	Status
EP receptor	PGE ₁ (Caverjet TM , Edex TM)	Pharmacia, Schwarz Pharma	Marketed
VIP receptor/ Adrenergic	VIP-phenolamine (Invicorp TM)	Senetek	Marketed outside US
K channels	PNU 83757	Pharmacia	Phase II

D. Intraurethral agents

Approach	Compound/Product	Company(ies)	Status
EP receptor	PGE ₁ (Muse TM)	Vivus, Abbott	Marketed

E. Topical

Approach	Compound/Product	Company(ies)	Status
EP receptor	PGE ₁ (Alprox-TD, Topiglan)	NexMed, MacroChem	Phase II and III

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MAR. 13. 2001 12:29PM

NO. 2199 P. 2/3

Brian J. Smith
Assistant Secretary and Divisional Vice President
Domestic Legal Operations
Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064

March 13, 2001

John Hancock Life Insurance Company
Investors Partner Life Insurance Company
John Hancock Variable Life Insurance Company
Attention: Stephen J. Blewitt
John Hancock Place
P.O. Box 111
Boston, MA 02117

Ladies and Gentlemen,

I have acted as counsel for Abbott Laboratories, an Illinois corporation (the "Company"), in connection with the Company's collaboration with John Hancock Life Insurance Company, a Massachusetts corporation, Investors Partner Life Insurance Company, a Massachusetts corporation, John Hancock Variable Life Insurance Company, a Delaware corporation (collectively, "John Hancock") pursuant to the Research Funding Agreement made as of March 13, 2001 (the "Research Funding Agreement"). Capitalized terms used herein without definition have the meanings assigned to them in the Research Funding Agreement.

In connection with the opinions expressed herein, I have made such examination of matters of law and of fact as I considered appropriate or advisable for purposes hereof. As to matters of fact material to the opinions expressed herein, I have relied upon certificates and statements of government officials and of officers of the Company. I have also examined originals or copies of such corporate documents or records of the Company as I have considered appropriate for the opinions expressed herein. I have assumed for the purposes of this opinion the genuineness of all signatures (other than those of individuals signing on behalf of the Company which are genuine), the legal capacity of natural persons, the authenticity of the documents submitted to me as originals, the conformity to the original documents of all documents submitted to me as certified, facsimile or photostatic copies, and the authenticity of the originals of such copies.

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JH 008210

MAR. 13. 2001 12:29PM

NO. 2199 P. 3/3

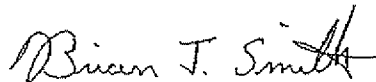
John Hancock Life Insurance Company
Investors Partner Life Insurance Company
John Hancock Variable Life Insurance Company
March 13, 2001
Page 2

Based upon the foregoing, and subject to the qualifications and limitations stated herein, I am of the opinion that: (i) the Company is duly organized, validly existing and in good standing in the State of Illinois; (ii) the Company has the requisite corporate power and authority to execute, deliver and perform the Research Funding Agreement; (iii) the Research Funding Agreement has been duly and validly authorized by the Company, and duly executed and delivered by an authorized officer of the Company and constitutes a valid and binding legal obligation of the Company enforceable against it in accordance with its terms; (iv) the performance of the Research Funding Agreement by the Company does not constitute a breach or violation of its organizational documents or any other agreement or understanding, written or oral, to which the Company is a party or any existing law, statute, rule or regulation by which the Company is bound; (v) no consents or approvals of any court or governmental authority is required on the part of the Company in connection with the execution, delivery, and performance of the Research Funding Agreement; (vi) there is no litigation pending, or to my knowledge threatened, which calls into question the validity of the Research Funding Agreement.

My opinion expressed above is limited to the law of the State of Illinois and the federal law of the United States, and I do not express any opinion herein concerning any other law.

The opinion set forth herein is rendered only to you and solely for your benefit in connection with the above described transactions. This opinion may not be relied upon by you for any other purpose, or relied upon by any other person for any purpose, without my prior written consent.

Very truly yours,



EX. 34



Abbott Laboratories

SEP 26 2003

BOND & CORP. FINANCE GROUP



Global Pharmaceutical Research & Development

Thomas Lyons
GPRD Controller
GPRD Finance
Dept. R404, AP9

Abbott Laboratories
100 Abbott Park Road
Abbott Park, Illinois 60064-6120

Telephone: (847) 937-5618
Fax: (847) 938-9609
Email: Thomas.Lyons@Abbott.com

September 22, 2003

Mr. Steven Blewitt
John Hancock Life Insurance Co.
200 Claredon Street, T-57
Boston, MA 02117

Attention: Bond & Corporate Finance Group

Re: Final 2003 Development Plans

Dear Steve:

Enclosed per your request are the Portfolio Program and Development cost summaries for the Final 2003 Plan.

Also, I went back to review the data and spend estimates made about 1 year ago for 2003. On 8/26/02, the estimated program spend for 2003 was at \$132.6 mm. By October 14, 2002, after the Executive Committee's portfolio review, the estimated spend for 2003 had dropped to \$109.9 mm and for 2004, it was at \$136.9 mm.

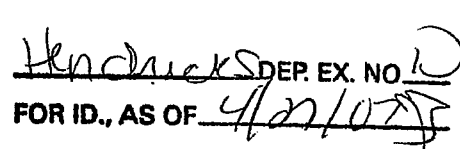
If you have any questions, please call me or Ken Stiles (at 847-938-6587).

Sincerely,


Tom Lyons
GPRD Controller
GPRD Finance

cc: Ken Stiles

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JH 001071


HENDERSON DEP. EX. NO 10
FOR ID., AS OF 4/27/03

John Hancock Portfolio
9/22/03
(\$mm)

	2003 Plan	
	Preliminary	Final
ABT 627		
· Base	55.5	52.6
· Early PCA	2.7	2.6
· Japan	3.2	1.9
· Non PCA	9.8	8.7
Total	71.2	65.8
ABT 510	18.3	18.2
ABT 751	10.7	10.2
ABT 773	1.7	1.7
ABT 492	7.2	4.9
ABT 724	0.1	0.1
Management Fee	2.0	2.0
Total Portfolio	111.2	102.9
10 mth.		Prelim.
2001		2004
171.7		96.7
2002		2005
141.3		142.7
2003 Plan		
102.9		
Total Portfolio Spend*		

* Includes Mgmt Fees/Milestones

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[illegible]

ACT OUTPULATED IN 3 PLANNING COST STUDIES. CURRENTLY IN 1971, 1972, 1973, 1974, 1975, 1976, 1977, 1978, 1979, 1980, 1981, 1982, 1983, 1984, 1985, 1986, 1987, 1988, 1989, 1990, 1991, 1992, 1993, 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463, 2464, 2465, 2466, 2467, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2649, 2

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ABT-627 (Atrasentan) Base Program

<u>External:</u>			<u>2003 Plan (000s)</u>	
<u>New Clinical Activities:</u>			<u>Total Patients</u>	<u>Enrolled</u>
<u>HEOR Studies</u>			<u>Start</u>	<u>End</u>
			1/1/03	12/31/03
				\$583
				\$583
<u>Ongoing Clinical Activities:</u>				
<u>Subtotal New Clinical Activities:</u>				
M00-211 Phase III (VW Metastatic Prostate Cancer)	900	808	5/1/01	2/1/04
M00-244 Phase II (VW nonmetastatic Prostate Cancer)	900	897	6/1/01	3/1/04
M00-258 Phase III (Ext for M00-244/M00-211)	1400	261	7/1/01	2/1/05
M01-304 Phase II Long Term Safety	250	26	10/15/01	3/1/05
Phase II - Bisphosphonate Combination	200		12/31/02	12/30/04
				\$628
<u>Subtotal Ongoing Clinical Activities:</u>				\$27,260
<u>CMC</u>				
PARD				\$830
Process R&D				\$50
<u>Pre-Clinical Safety Support</u>				
Pre-Clinical Safety Support				\$104
			Total External	\$28,827
<u>Internal</u>			<u>FTE</u>	<u>(\$000s)</u>
<u>Clinical Program</u>				
Global Project Mgmt			39.9	\$8,067
Phase I Center Support			1.3	\$282
European Clinical Organization			4.1	\$554
Data Management/Statistics			21.9	\$3,769
<u>Chemistry, Manufacturing and Controls (CMC)</u>				
Formulation (PARD)			5.5	\$1,491
Analytics for Formulation(PARD)			7.2	\$1,952
Analytics for Process Chemistry (PARD)			3.6	\$883
Clinical Packaging(PARD)			2.0	\$535
Process R&D			6.0	\$2,233
<u>Drug Safety Support</u>				
Toxicology/Pathology			1.8	\$489
Metabolism			2.3	\$614
Other			0.3	\$107
<u>Other Support Cost</u>				
Discovery (Therapeutic Discovery)			0.5	\$138
Medical Services				\$165
Research Quality Assurance			2.8	\$775
Medical Affairs			1.0	\$168
Regulatory Affairs				\$1,211
Other			0.9	\$227
			Total Internal	\$23,760
			Total Program:	\$52,587

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ABT-627 Indication For Early - Stg PCA

<u>External:</u>				<u>2003 Plan (\$000s)</u>	
<u>Ongoing Clinical Activities:</u>					
M01-366 Phase II Hormone Naive					
<u>Total Patients</u>	<u>Enrolled</u>	<u>Start</u>	<u>End</u>		
200	22	4/1/02	1/1/05		\$2,256
Subtotal Ongoing Clinical Activities:					\$2,256
Total External					\$2,256
<u>Internal:</u>				<u>FTE (\$000s)</u>	
<u>Clinical Program</u>					
Global Project Mgmt				1.0	
Phase I Center Support				0.1	\$21
Data Management/Statistics				0.6	\$98
<u>Chemistry, Manufacturing and Controls (CMC)</u>					
Clinical Packaging(PARD)				0.3	\$90
<u>Drug Safety Support</u>					
Metabolism				0.3	\$68
<u>Other Support Cost</u>					
Medical Services					\$10
Research Quality Assurance				0.1	\$25
Other				-0.1	\$(1)
Total Internal				2.3	\$311
Total Program:					\$2,567

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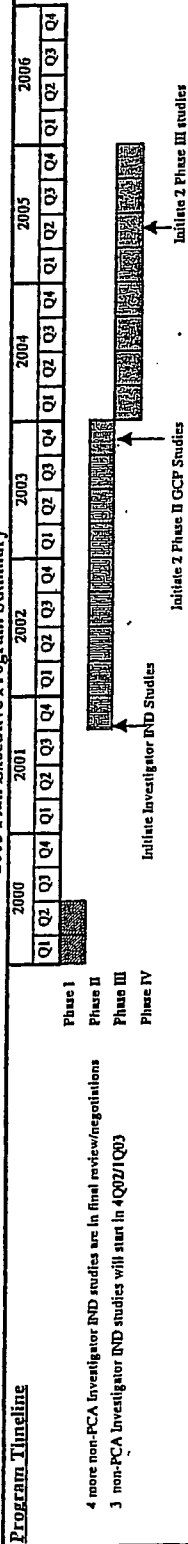
ABT - 627 Japan Registration

<u>External:</u>				<u>2003 Plan (\$000s)</u>	
<u>Ongoing Clinical Activities:</u>					
Japan Phase I Pharmacokinetic Study - Prostate Cancer					\$1,514
<u>Subtotal Ongoing Clinical Activities:</u>					\$1,514
	<u>Total Patients</u>	<u>Enrolled</u>	<u>Start</u>	<u>End</u>	
	48	0	3/1/03	1/1/03	
	<u>Total External</u>				\$1,514
<u>Internal</u>				<u>FTE</u>	<u>(\$000s)</u>
<u>Clinical Program</u>					
Global Project Mgmt				0.3	
Phase I Center Support				0.4	\$85
Data Management/Statistics				0.5	\$90
<u>Chemistry, Manufacturing and Controls (CMC)</u>					
Clinical Packaging (PARD)				0.2	\$60
<u>Drug Safety Support</u>					
Metabolism				0.6	\$163
<u>Other Support Cost</u>					
Research Quality Assurance				0.1	\$30
Other				0.0	\$1
	<u>Total Internal</u>				\$429
<u>Total Program:</u>					\$1,943

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ABT-627 Non-Prostate Cancers

2003 Plan Executive Program Summary

**2003 Clinical Program Objectives:**

Initiate 7 Investigator IND studies in Lung, Ovarian, Colorectal, Pancreas, Breast and Renal cancers
 Assume two cancer types will yield a signal of activity from investigator INDs and initiate phase II/III studies (with interim analysis)

(000's \$)
 Plan
2003 PROGRAM COST
8,670.0

Description of Internal Activities:

Data Management/Statistics:
 Review Investigator IND study protocols and provide comments
 Prepare/review protocols and case report forms for four Phase II studies
CMC: Formulation and Analytical Package
 Package and ship clinical supplies as required for up to 20 ongoing Investigator IND studies.
 Produce clinical supplies for 4 Phase II studies

Program Status

Original objective of the Investigator IND studies was to allow testing of ABT-627 in cancers not being currently investigated by Abbott
 Original number of planned Investigator IND studies considered was 12-15.
 Number of Investigator IND studies now increased to 20 in cancers other than prostate
 Plan expanded for 2003 to include formal development of ABT-627 in the two most promising non-prostate cancers

LRP

2001	2002	2003	2004	2005	Future Yrs	Total
\$ -	\$ -	\$ 8.7	\$ 2.8	\$ 9.6	\$ 147.0	\$ 168.1

LABORATORY PLANNING COST SUMMARY - Copy Page 10 of 103 - CONFIDENTIAL DOC#ABT-627 Non-PCA Dec 1003 Pgs 112-113 (Rev 3/04)

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ABT - 627 Non - PCA Cancers

<u>External:</u>				<u>2003 Plan (000s)</u>	
				<u>Total Patients</u>	<u>Enrolled</u>
				<u>Start</u>	<u>End</u>
New Clinical Activities:					
Phase II trial #1				50	0
Phase II trial #2				50	
Investigator IND Studies 2003					
Subtotal New Clinical Activities:					
Ongoing Clinical Activities:					
Investigator IND Studies 2002				12/1/01	6/30/03
Subtotal Ongoing Clinical Activities:					
				Total External	\$7,320
<u>Internal:</u>				<u>FTE</u>	<u>(\$000s)</u>
Clinical Program					
Phase I Center Support				0.5	\$105
Data Management/Statistics				3.2	\$538
Chemistry, Manufacturing and Controls (CMC)					
Clinical Packaging(PARD)				0.9	\$231
Drug Safety Support					
Metabolism				1.6	\$432
Other Support Cost					
Research Quality Assurance				0.2	\$44
Other				-0.1	-
Total Internal				6.3	\$1,350
Total Program:					\$8,670

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TSP #1 (ABT-510)
2003 Update Executive Program Summary - Funded Program

Program Timeline																2003 PROGRAM COST											
																(\$000's)											
																Plan											
																18,239.0											

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ABT-510 (TSP Peptide) Base Program

External:				2003 Plan (000s)	
				Total Patients	Enrolled
				Start	End
New Clinical Activities:					
M02-534 Phase II Sarcoma				12/2/02	12/1/03
Cancer Models				5/1/03	1/31/04
				60	\$1,212
					\$297
					\$1,509
Subtotal New Clinical Activities:					
Ongoing Clinical Activities:					
M02-429 Phase II Lung Cancer				11/4/02	11/3/03
M02-457 Phase II Lymphoma				12/2/02	12/1/03
M02-428 Phase II Renal Cancer				12/10/02	12/10/03
M01-302 Multiple Low Dose				37	\$769
Phase II Breast Cancer Combination				12/4/01	12/10/03
Phase IIb/III Trial In NSCLC				1/6/03	1/5/04
Cancer Models 2002				1/15/04	\$595
				7/1/02	\$532
					\$444
					\$118
					\$5,258
Subtotal Ongoing Clinical Activities:					
CMC					
PARD					\$388
Process R&D					\$35
Pre-Clinical Safety Support					
Pre-Clinical Safety Support					\$1,134
					\$8,324
				Total External	
Internal:				FTE (\$000s)	
Clinical Program					
Global Project Mgmt				6.9	\$2,632
Phase I Center Support				1.7	\$361
European Clinical Organization				0.9	\$127
Data Management/Statistics				6.4	\$1,150
Chemistry, Manufacturing and Controls (CMC)					
Formulation (PARD)				1.0	\$239
Analytics for Formulation(PARD)				1.8	\$475
Analytics for Process Chemistry (PARD)				0.9	\$239
Clinical Packaging(PARD)				3.9	\$1,030
Process R&D				1.8	\$979
Drug Safety Support					
Toxicology/Pathology				1.4	\$380
Metabolism				4.2	\$1,146
Other				0.5	\$136
Other Support Cost					
Discovery (Therapeutic Discovery)				1.4	\$372
Medical Services					\$75
Research Quality Assurance				1.7	\$449
Regulatory Affairs					\$125
Other				-0.1	-
				Total Internal	\$9,915
				Total Program:	\$18,239

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2003 Prior Executive Program Summary													2003 PROGRAM COST															
													(2003) Plan															
													10,228															
<p>Program Timeline</p> <p>NDA filing delayed for 1 year, from 3Q 05 to 3Q 06, due to funding decision 10/02.</p> <p>Development plan for 2003 reduced from seven Phase I studies to four to meet budgetary target.</p> <p>Initiation of Phase II delayed due to extended initiation of Phase I testing; good tolerability allowed testing of higher doses for longer intervals; i.e., 21 days CMC for Phase III delayed to 4Q03 after GONOGO</p> <p>Initiation 7-day and 21-day Ph I</p> <p>Ph I Pediatric study-NCI</p> <p>Ph II Leukemia and Breast</p> <p>Ph II Renal and NSCLC</p> <p>Ph II Colorectal Cancer</p> <p>End of Ph II Mfg.</p> <p>FDA Test Mfg.</p> <p>Inform 1st Ph III</p> <p>Inform 2nd Ph III</p> <p>NDA (m leukaemia)</p> <p>Launch</p>																												
2003 Clinical Program Objectives:																												
Complete enrollment in two Phase I studies by 3/03. Pediatric trial continues into 2004.																												
Complete enrollment in three Phase II studies in various cancer types by 6/03 (Breast, NSCLC and Renal (Step 1)) and one Ph II study by 9/03 (Colorectal).																												
Complete enrollment in collaborative study in Leukemia by 9/03.																												
Go/No Go decision on Phase III in 9/03.																												
End of Phase II meeting with FDA in 12/03.																												
Description of Internal Activities:																												
DM/Statistics: Complete data entry and statistical analysis of two Phase I clinical trials by 10/03. Complete data entry and statistical analysis of one Phase II trial (NSCLC) by 12/03. Develop ORFs for colorectal Phase II clinical trial by 3/03.																												
CMC: ABC/Process Development Manufacture additional drug substance for process development, clinical supplies and formulation activities in 4Q 03 if Go to Phase III. Formulation and Analytical Identify facility for registration/commercial production of drug product by 12/03.																												
Drug Safety: Complete drug analysis and PK summary for two Phase I studies by 11/03. Develop protocol for a six-cycle (six month studies, 1/04 start date) and toxicology studies in rats and dogs by 12/03. Protein binding studies (5 species), tissue distribution and metabolic fate in rats and dogs by 12/03.																												
Discovery: Initiate animal model studies to explore combination therapy regimens in support of clinical development plan. Develop/validate biomarkers predictive of therapeutic response by 12/03																												
Regulatory: Complete discussions with FDA on need for additional toxicology testing by 6/03. Arrange end of Phase II meeting with FDA in 12/03 to discuss Ph II plan.																												
Program Status:																												
Due to equipment/facility containment issues, work on a tablet formulation has been suspended; Phase III and Commercial will use a capsule formulation.																												
Planned additional toxicology studies may not be needed depending on discussions with FDA. Discussions planned for 6/03.																												
Phase I studies have determined PK in non-Asian population.																												
MTD of 300 mg QD 7-day dosing established.																												
Phase I studies continue in 7-day (BID only) and 21-day (QD and BID) dosing to esia																												
7 Day Dosing: 2 patients had Stable Disease for 6 cycles, one at 300 mg QD, one at 250 QD, Highest BID dose to date 150 mg.																												
21 Day Dosing: 1 patient had Stable Disease (25 mg QD) and 1 had Partial Response (50 mg QD) each for 6 cycles so far. Highest dose to date 200 mg QD, 100 mg BID																												
NCI pediatric trial enrolling (6 patients as of 11/02).																												
<table><tr><th>2001</th><th>2002</th><th>2003</th><th>2004</th><th>Total</th></tr><tr><td>\$ 6.5</td><td>\$ 9.6</td><td>\$ 10.2</td><td>\$ 36.0</td><td>\$ 132.7</td></tr><tr><td></td><td></td><td></td><td>\$ 48.0</td><td>\$ 231.0</td></tr></table>														2001	2002	2003	2004	Total	\$ 6.5	\$ 9.6	\$ 10.2	\$ 36.0	\$ 132.7				\$ 48.0	\$ 231.0
2001	2002	2003	2004	Total																								
\$ 6.5	\$ 9.6	\$ 10.2	\$ 36.0	\$ 132.7																								
			\$ 48.0	\$ 231.0																								

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ABT-751 Base Program

<u>External:</u>	<u>Total Patients</u>	<u>Enrolled</u>	<u>Start</u>	<u>End</u>	<u>2003 Plan (\$000s)</u>
Ongoing Clinical Activities:					
M02-447 Phase II (Breast)	40		10/1/02	10/1/03	\$785
M02-448 Phase II (Lung Cancer)	30		11/1/02	11/1/03	\$324
M02-446 Phase II (Colorectal Cancer)	30		12/1/02	12/1/03	\$492
M02-416 Phase II (Renal Cancer)	60		11/1/02	11/1/03	\$336
Subtotal Ongoing Clinical Activities:					\$1,937
CMC					
PARD					\$15
Process R&D					\$130
			Total External		\$2,082
<u>Internal</u>				<u>FTE</u>	<u>(\$000s)</u>
Clinical Program					
Global Project Mgmt				6.4	\$2,121
Phase I Center Support				1.1	\$226
European Clinical Organization				0.4	\$54
Data Management/Statistics				4.5	\$636
Chemistry, Manufacturing and Controls (CMC)					
Formulation (PARD)				3.1	\$841
Analytcs for Formulation(PARD)				3.5	\$948
Analytcs for Process Chemistry (PARD)				1.8	\$478
Clinical Packaging(PARD)				0.8	\$217
Process R&D				2.2	\$1,183
Drug Safety Support					
Toxicology/Pathology				0.2	\$49
Metabolism				2.1	\$573
Other				0.2	\$64
Other Support Cost					
Discovery (Therapeutic Discovery)				0.5	\$149
Medical Services					\$29
Research Quality Assurance				1.0	\$274
Medical Affairs				0.1	\$17
Regulatory Affairs					\$84
Other				0.0	\$(1)
			Total Internal	27.9	\$8,144
			Total Program:		\$10,226

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**ABT-773 Base
2003 Plan Executive Program Summary**

Program Timeline																												2003 PROGRAM COST (000's) Plan <u>1,367.0</u>
2000				2001				2002				2003				2004				2005				2006				
Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
Phase I												Phase II																
Phase II												Phase III																
Phase III												Phase IV																
												<p>Completion of all report filing in RIC</p> <p>QT Phase I Results</p> <p>All Phase I reports complete</p> <p>M00-219 CAP</p> <p>M00-216 ABECB Results</p> <p>M00-222 ASP EU results</p> <p>Prepare all reports to support outlicensing</p> <p>M00-217 ABECB EU results</p>																

2003 Clinical Program Objectives:

Complete clinical study report for M00-217 ABECB in Europe
 Complete data classification, stats analysis and clinical study report for M00-222 Pharyngitis in Europe.
 Complete final reconciliation of all clinical study external expenses.
 Provide support for annual IND update
 Provide support for due diligence activities for the Licensing group.

Description of Internal Activities:

Support bulk drug and final product stability program (24 mo timepoint) as per FDA end-of-Phase II agreement

Program Status:

US and European development will not continue while out licensing partner being sought.

2001	2002	2003	2004	2005	Future Yrs	Total
\$ 80.3	\$ 13.8	\$ 1.4	\$ -	\$ -	\$ -	\$ 95.5

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<u>ABT-773 Base Program</u>				
<u>External:</u>	<u>Total Patients</u>	<u>Enrolled</u>	<u>Start</u>	<u>End</u>
CMC				
PARD				
	<u>Total External</u>			<u>2003 Plan (\$000s)</u>
				\$10
				\$10
<u>Internal:</u>				
		<u>FTE</u>		<u>(\$000s)</u>
Clinical Program				
Global Project Mgmt		1.4		\$294
Phase I Center Support		0.1		\$11
Data Management/Statistics		0.4		\$82
Chemistry, Manufacturing and Controls (CMC)				
Formulation (PARD)		0.8		\$215
Analytics for Formulation(PARD)		1.2		\$330
Analytics for Process Chemistry (PARD)		0.5		\$166
Clinical Packaging(PARD)		0.4		\$89
Drug Safety Support				
Other		0.2		\$54
Other Support Cost				
Research Quality Assurance		0.2		\$58
Regulatory Affairs				\$59
Other		-0.1		\$(1)
	<u>Total Internal</u>	<u>5.2</u>		<u>\$1,357</u>
	<u>Total Program:</u>			<u>\$1,367</u>

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ABT-773 Japan
2003 Plan Executive Program Summary

Program Timeline													2003 PROGRAM COST (\$000's) Plan 336.0		
2000		2001		2002		2003		2004		2005		2006			
Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
<div>Phase I Phase II Phase III Phase IV</div> <div>M00-219 CAP M00-216 ABECB Results Japan CAP Open Label Results Ketek price is known Kiko Meeting in Japan QT Phase I Results Launch 1Q 2008 NDA</div>															
2003 Clinical Program Objectives:															
Obtain agreement with KIKO regarding dose decision and clinical program strategy. Phase IIb CAP Dose Ranging study postponed until KIKO feedback obtained and Ketek pricing is available Phase I PK evaluation of clinical dose postponed until KIKO feedback obtained and Ketek pricing is available. Phase I evaluation of fatty liver vs normals to satisfy Japan opinion leader, as requested by Taisho and Daiichibot. Postponed until KIKO feedback obtained and Ketek pricing is available															
Description of Internal Activities:															
Initiate minimal process transfer support with Taisho for final product manufacture. Provide bulk drug inventory support for final product transfer activities with Taisho and meet Japanese requirements. Initiate methods development to support Japan final dose. Manufacture clinical supplies for Phase IIb.															
Program Status:															
Continue dialogue with partner company Taisho on ABT-773 program viability and strategies. ABT-773 development in Japan is a non-bridging strategy following the decision on US/EU development and subsequent outlicensing plan. A meeting with KIKO is urgent to obtain feedback on dose decision, acceptability of western safety data and clinical program strategy. Initiation of Phase IIb study in 1Q 2003 is important to provide continuing development activities with key investigators in Japan, particularly given Avelis activity. Japanese development will continue at a minimal level while an outlicensing partner is being negotiated.															
CONFID JH 00															
2001		2002		2003		2004		2005		Future Yrs		Total			
\$ 1.4		\$ 1.9		\$ 0.3		\$ -		\$ -		\$ -		\$ 3.6			

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ADT 773 JAPAN
2003 Plan Development Cost Summary

<u>External:</u>		
Total External		
<u>Internal:</u>		
Clinical Program	Plan FTE's	2003 Plan
Global Project Management	0.35	\$76
Chemistry, Manufacturing, and Controls (CMC)	0.40	\$109
Formulation and Analytical (FARD)	0.50	\$151
Process Chemistry		
Total Internal	1.25	\$336
Total Program		\$336
		NOTE: Talaho will share 50% of these costs.

1431001 Final ADT 773 JAPAN DCE 04 Jul 04 Conf Rev

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ABT-492
2003 Plan Executive Program Summary

Program Timeline		2000	2001	2002	2003	2004	2005	2006	2003 PROGRAM COST
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	
Phase I									(000's) Plan 4,853.0
Phase II									
Phase III									
Formulation development									

2003 Clinical Program Objectives:

492 Base
 Complete enrollment on clinical studies M01-288 & M01-344
 Complete data classification, stats analysis and clinical study reports for M01-288 AECEB, M01-344 CAP & M01-365 QTC assessment studies.
 Complete final reconciliation of all clinical study external expenses.
 Provide support to annual IND update.

492 IV
 There are no clinical activities planned for 2003

Description of Internal Activities:

Complete all ongoing toxicology studies.
 Close out all existing CMC work with full documentation completed.

Program Status:

Owing to the rationalization of development funding, the ABT-492 project will not be continued beyond Phase II at this point in time.
 Funding for 2003 will be reduced to a level adequate to finish existing work (to maintain project value) and comply with FDA requirements.
 No new clinical or toxicological studies will be initiated.
 There will be no new CMC activities

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LRP		Future Yrs		Total
2001	2002	2003	2004	2005
\$ 20.1	\$ 28.2	\$ 4.9	\$ 0.9	\$ -
				\$ 54.1

ABT-492 Outrolone

External:				2003 Plan (000s)	
Ongoing Clinical Activities:				Start	End
WBC Study				Total Patients Enrolled	
					\$250
					\$250
Subtotal Ongoing Clinical Activities:				Total External	\$250
Internal				FTE	(\$000s)
Clinical Program					
Global Project Mgmt				9.3	\$2,028
Phase I Center Support				0.5	\$101
Data Management/Statistics				2.7	\$488
Chemistry, Manufacturing and Controls (CMC)					
Formulation (PARD)				0.8	\$174
Analytics for Formulation (PARD)				0.3	\$74
Analytics for Process Chemistry (PARD)				0.1	\$37
Clinical Packaging (PARD)				0.3	\$73
Process R&D				0.7	\$188
Drug Safety Support					
Toxicology/Pathology				0.1	\$27
Metabolism				1.8	\$513
Other Support Cost					
Discovery (Therapeutic Discovery)				2.0	\$651
Medical Services					\$10
Research Quality Assurance				0.9	\$228
Medical Affairs				0.2	\$25
Regulatory Affairs					\$77
Other				-0.3	\$1
Total Internal				19.5	\$4,803
Total Program:					\$4,853

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ABT-724 (Dopamine 4 Agonist) Base Program

<u>Internal</u>		<u>FTE</u>	<u>(\$000s)</u>
Clinical Program			
Global Project Mgmt			
Total Internal			\$75
Total Program:			\$75

$\frac{2001}{0.6}$ $\frac{2002}{5.5}$ $\frac{2003}{0.1}$ $\frac{2004}{-}$ $\frac{2005}{-}$

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EX. 43

2 ABBOTT

Abbott Laboratories
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

November 16, 2004

VIA FAX and U.S. MAIL

John Hancock Financial Services, Inc.
John Hancock Place
Post Office Box 111
Boston, Massachusetts 02117
Attn: Stephen J. Blewitt,
Senior Managing Director

Re: Research Funding Agreement Between Abbott Laboratories
("Abbott") and John Hancock Life Insurance Company, John
Hancock Variable Life Insurance Company and Investors Partner
Life Insurance Company (collectively, "John Hancock") Dated
March 13, 2001 (the "Agreement")

Dear Mr. Blewitt:

In accordance with Sections 1.6 and 2.2 of the Agreement, enclosed please find Abbott's preliminary Annual Research Plan for 2005. Please note that the Plan sets forth Abbott's estimated spending of \$149.8 million provided Abbott receives Hancock's payments due under the Agreement in December 2004. If Hancock refuses to fund its portion of Program Costs under the Agreement, Abbott estimates spending during 2005 to be approximately \$87 million less than shown. In either event, Abbott's spending will exceed its \$400 million portion of the Aggregate Spending Target independent of Hancock's payments to date.

In addition, in accordance with Section 2.5 of the Agreement, please also find the research report concerning the status of the Research Program and all Program Related Costs expended by Abbott for the first ten (10) months of 2004, together with good faith estimates for the last two (2) months of 2004.

ABBT 0027246

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Hendricks DEP EX. NO. 12
FOR ID., AS OF 4/27/07



John Hancock Financial Services, Inc.
November 16, 2004
Page 2

Very truly yours,


James L. Tyree

cc: VIA FAX and U.S. MAIL
John Hancock Life Insurance Company
200 Clarendon Street, T-57
Boston, MA 02117
Attn: Bond & Corporate Finance Group

VIA FAX and U.S. MAIL
John Hancock Life Insurance Company
200 Clarendon Street, T-50
Boston, MA 02117
Attn: Investment Law Division

ABBT 0027247

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Global Pharmaceutical Research & Development
 Hancock Development Collaboration Portfolio
 Spending by Program

	In millions of dollars				
	2001	2002	2003	2004	2005*
ABT-100 FTI	3.6	2.4	0.0	0.0	0.0
ABT-492 Quinolone	20.1	28.2	4.1	0.6	0.0
ABT-510 TSP #1	8.8	12.3	18.5	23.0	44.7
ABT-518 MMPI	3.7	0.0	0.0	0.0	0.0
ABT-594 Neuro Pain	7.8	1.4	0.0	0.0	0.0
ABT-627 Abiraterone Base	34.1	48.1	50.7	36.2	58.2
ABT-627 Abiraterone Hormone Naive Prostate Cancer	0.0	1.2	2.5	2.3	7.1
ABT-627 Japan	0.0	0.1	0.2	2.0	3.9
ABT-627 Non-Prostate Cancers	0.0	0.0	0.2	1.4	6.0
ABT-724 Disqualine 4 Agonist	3.2	5.5	0.8	0.0	0.0
ABT-731 Anti-Mitotic	6.5	9.6	11.0	16.3	20.9
ABT-773 Ketolide Base	80.3	13.8	(0.9)	0.4	0.0
ABT-773 Ketolide Japan	1.4	1.9	0.0	0.0	0.0
Other	2.2	6.8	0.0	0.0	0.0
Total Program Spend	171.7	131.3	87.4	82.2	149.8
Management Fee / Milestones	0.0	10.0	2.0	2.0	0.0
Grand Total Cash Flow	171.7	141.3	89.4	84.2	149.8
Cumulative					
ABT-100 FTI	3.6	6.0	6.0	6.0	6.0
ABT-492 Quinolone	20.1	48.3	52.4	53.0	53.0
ABT-510 TSP #1	8.8	21.1	39.6	62.6	107.3
ABT-518 MMPI	3.7	3.7	3.7	3.7	3.7
ABT-594 Neuro Pain	7.8	9.2	9.2	9.2	9.2
ABT-627 Abiraterone Base	34.1	82.2	132.9	169.1	227.3
ABT-627 Abiraterone Hormone Naive Prostate Cancer	0.0	1.2	3.7	6.0	13.1
ABT-627 Japan	0.0	0.1	0.3	2.3	6.2
ABT-627 Non-Prostate Cancers	0.0	0.0	0.2	1.6	7.6
ABT-724 Disqualine 4 Agonist	3.2	8.7	9.5	9.5	9.5
ABT-731 Anti-Mitotic	6.5	16.1	27.1	43.4	73.3
ABT-773 Ketolide Base	80.3	94.1	93.2	93.6	93.6
ABT-773 Ketolide Japan	1.4	3.3	3.3	3.3	3.3
Other	2.2	9.0	9.0	9.0	9.0
Total Program Spend	171.7	303.0	390.1	478.3	631.1
Management Fee / Milestones	0.0	10.0	12.0	14.0	14.0
Grand Total Cash Flow	171.7	313.0	402.1	492.3	645.1

* Assumed receipt of Hancock's remaining payments in Dec-2004

ABBT 0027248

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Global Pharmaceutical Research & Development
Hancock Funding Agreement
Spending by Program
In millions of dollars

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	Month 10 YTD 2004	Mo. 11 & 12 LBE 2004	Total Year 2004
ABT-492	0.6	0.0	0.6
ABT-510	18.9	4.1	23.0
ABT-627 Afresentan Base	31.6	4.6	36.2
ABT-627 Afresentan Hormone Naive Prostate Cancer	1.8	0.5	2.3
ABT-627 Japan	1.2	0.8	2.0
ABT-627 Non-Prostate Cancers	0.8	0.6	1.4
ABT-751	11.4	4.9	16.3
ABT-773	0.4	0.0	0.4
Total Program Spend	66.7	15.5	82.2
Management Fee		2.0	2.0
Grand Total Cash Flow	66.7	17.5	84.2

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GPDR 2003 Plan
Araucanian HRP/CA Expanded Access Program ABY627

<u>External:</u>		<u>Total Patients</u>		<u>Start</u>	<u>End</u>	<u>2003 Plan \$(000s)</u>
Clinical Activities:						
MiniAAA HRP/CA Expanded Access Program		1400		04/05	03/07	\$7,289
Subtotal Clinical Activities:						\$7,289
Clinical Program						
Total External						\$7,289
<u>Internal:</u>		<u>2003 Plan FTEs</u>		<u>\$(000s) Chargeable</u>		<u>2003 Plan \$(000s)</u>
Clinical Program				<u>Payroll</u>	<u>Variable</u>	<u>Fixed</u>
Global Project Mgmt		1.2		\$188	\$81	\$14
European Clinical Organization		0.0			\$44	
Data Management/Statistics		3.2		\$354	\$24	\$39
Global Drug Supply		2.9		\$270	\$118	\$30
Pre-Clinical Safety Evaluation		0.0		\$0	\$0	\$0
Metabolism		0.0		\$0	\$0	\$0
Other Support Cost		0.2		\$20	\$7	\$1
Research Quality Assurance		4.2				
Total Internal						\$4,812
Total Project:						\$9,101

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GPRD 2005 Plan
Assessment - Mouse and Rat Carcinogenicity ABT 627

		Total Patients		Start	End	2005 Plan \$(000s)
<u>Externals:</u>						
Pre-Clinical Safety Evaluation						\$0
Pre-Clinical Safety Evaluation						\$750
Other Support Cost						\$750
Global Project Management						
		Total External				
<u>Internal:</u>						
		2005 Plan FTEs				2005 Plan \$(000s)
Clinical Program			Payroll	Variable	Fixed	Overhead
Global Project Mgmt	0.0		\$3			\$4
Data Management/Statistics	0.0					
Pre-Clinical Safety Evaluation	2.3		\$250	\$110	\$140	\$204
Toxicology/Pathology	0.0		\$60	\$20	\$30	\$52
Metabolism	0.0					
Other	0.1		\$12	\$7	\$4	\$6
Other Support Cost	0.1		\$17	\$5	\$1	\$12
Discovery (Therapeutic Discovery)	0.1					
Research Quality Assurance	0.1					
	3.1					
				Total Internal		\$975
				Total Program:		\$1,725

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GPDR 2005 Plan
Atrazenian - Non-PCA (ITT, Ph IIb and Japan) ABBT 627

External		Total Patients		Start	End	2005 Plan \$(000s)
Clinical Activities:						
NonAAV Phase IIB Trial 2 Ph II		60		1/05	0/07	\$538
NonAAV Phase IIB Trial 1 Ph II		60		0/05	6/07	\$1,388
Investigator IND studies		0		7/05	1/07	\$542
Subtotal Clinical Activities:						\$2,468
Clinical Program						\$1
Global Drug Supply						\$2,469
Total External						\$2,470
Internal		2005 Plan FTEs		2005 Plan \$(000s)		
Clinical Program						
Global Project Mgmt		2.7				\$764
European Clinical Organization		0.0				
Data Management/Statistics		0.6				\$150
Global Drug Supply		0.2				\$45
Pre-Clinical Safety Evaluation						
Metabolism		0.0				
Other Support Cost						
Research Quality Assurance		0.1				\$17
Total Internal		3.6		\$8		\$986
Total Program:						\$3,456

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GPB 2005 Plan
Abravanti - Early PCA M01-366 LT Extension ABT 627

External:		Total Patients	Start	End	2005 Plan \$1000s
Clinical Activities:					
M03522 Retrospective Tissue Collection for Vysis IHC analysis Ph II		0	105	7/05	\$850
Subtotal Clinical Activities:					\$850
Other Support Cost					
Global Project Management (M01-366 LT Extension)					\$2,700
Total External					\$3,550
Internal:		2005 Plan FTEs	Fixed	Overhead	Other
Clinical Program					
Global Project Mgmt		0.1	\$14	\$9	\$26
Data Management/Statistics		0.2	\$2	\$15	\$39
Total Internal		0.3			\$61
Total Program:					\$3,611

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NO.257 P.10

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GPRD 2005 Plan
Attachment - HRPC M00-244 Continuation ABT 627

<u>External:</u>		<u>Total Patients</u>		<u>Start</u>	<u>End</u>	<u>2005 Plan \$1000s</u>
Clinical Activities:						
M00244 WW nonmetastatic Prostate Cancer Ph III		941		6/04	6/05	\$1,300
Clinical Program						\$0
Global Drug Supply						\$0
Other Support Cost						\$0
Global Project Management						\$1,300
Total External						\$1,300
<u>Internal:</u>		<u>2005 Plan FTEs</u>		<u>\$1000s/Chargeable</u>		<u>2005 Plan \$1000s</u>
Clinical Program				<u>Fixed</u>	<u>Overhead</u>	<u>Other</u>
Global Project Mgmt	7.5	\$1,037	\$376	\$92	\$622	\$2,127
European Clinical Organization	0.9		\$176			\$176
Data Management/Statistics	3.3	\$322	\$21	\$35	\$333	\$710
Global Drug Supply	2.4	\$228	\$99	\$28	\$143	\$400
Pre-Clinical Safety Evaluation						
Metabolism	0.4	\$41	\$10	\$24	\$33	\$116
Other Support Cost						
Research Quality Assurance	0.4	\$44	\$14	\$2	\$32	\$91
	14.9					\$3,718
Total Internal						\$3,718
Total Program:						\$5,023

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NO. 257 P. 11

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**CFRD 2005 Plan
ABT731 - Ph IIb and Ph III Studies**

<u>External:</u>		<u>Total Patients</u>		<u>Start</u>	<u>End</u>	<u>2005 Plan \$000s</u>
Clinical Activities:						
NonAAQ Pivotal safety and efficacy 1 Ph III		400		5/05	8/07	\$4,005
Investigator Initiated Abbott Initiated Collaboration Trials Ph II		0		1/05	2/00	\$214
Discovery		0		1/05	12/05	\$100
						\$5,319
Subtotal Clinical Activities:						\$1,600
Clinical Program						
Global Drug Supply						\$100
Chemistry, Manufacturing and						\$400
PARC						
Process R&D						
Pre-Clinical Safety Evaluation						\$1,375
Pre-Clinical Safety Evaluation						
Other Support Cost						
Discovery						\$310
						\$9,104
						Total External
<u>Internal:</u>		<u>2005 Plan FTEs</u>		<u>\$000s Chargeable</u>		
				<u>Fixed</u>	<u>Overhead</u>	<u>Other</u>
Clinical Program						
Phase 1 Center Support		0.0	\$5	\$1	\$4	\$12
Global Project Mgmt		7.4	\$1,022	\$90	\$813	\$2,145
European Clinical Organization		2.0				\$541
Data Management/Statistics		1.4	\$139	\$15	\$144	\$307
Global Drug Supply		1.4	\$131	\$18	\$92	\$289
Chemistry, Manufacturing and Controls (CMC)						
Formulation (PARC)		1.4	\$182	\$80	\$127	\$429
Analyticals for Formulation (PARC)		2.0	\$201	\$129	\$102	\$611
Analyticals for Process Chemistry (PARC)		1.0	\$130	\$85	\$91	\$308
Parenteral & Advanced Drug Delivery		0.0				
Process R&D		8.2	\$932	\$688	\$434	\$3,497
Pre-Clinical Safety Evaluation						
Toxicology/Pathology		2.8	\$312	\$182	\$249	\$878
Metabolism		1.9	\$217	\$126	\$173	\$609
Other		0.3	\$36	\$21	\$29	\$101
Other Support Cost						
Discovery (Therapeutic Discovery)		1.8	\$193	\$89	\$94	\$474
Research Quality Assurance		2.0	\$258	\$10	\$108	\$541
		34.4			Total Internal	\$10,732
						\$19,835
						Total Program:

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NO. 257 P. 12

CONFIDENTIALGPRD 2005 Plan
ABT310 TSP Penide

<u>Internal</u>	<u>Total Patients</u>	<u>Start</u>	<u>End</u>	<u>2005 Plan \$000s</u>
Clinical Activities:				
OA Regulatory and GRT Support	0	1/05	12/05	\$200
M05MB Phase IIa ABT-810 + VEGF	40	3/05	2/07	\$750
M05AAA Phase IIa Colorectal Cancer	100	2/05	1/07	\$1,376
M04AAU Long term extension studies P1, II	355	2/05	1/08	\$740
M04711 Phase III Sarcoma P1, II	350	1/05	12/06	\$5,084
M02428 Phase II Renal Cancer P1, II	100	3/03	2/05	\$277
Subtotal Clinical Activities:				\$8,406
Clinical Program				
Global Drug Supply				\$2,700
Chemistry, Manufacturing and Controls (CMC)				
PARD				\$590
Process R&D				\$3,169
Pre-Clinical Safety Evaluation				
Pre-Clinical Safety Evaluation				\$1,262
Other Support Cost				
Other Services Purchase				\$865
Discovery				\$519
				\$17,295

Total External

<u>Internal</u>	<u>2005 Plan FTEs</u>	<u>\$000s Chargeable</u>	<u>Overhead</u>	<u>Other</u>	<u>2005 Plan \$000s</u>
		<u>Variable</u>	<u>Fixed</u>		
Clinical Program					
Global Project Mgmt	26.5	\$1,278	\$312	\$2,114	\$7,229
Phase 1 Center Support	2.1	\$71	\$48	\$205	\$581
European Clinical Organization	8.9	\$1,888	\$64	\$768	\$1,698
Data Management/Statistics	7.7	\$48	\$90	\$461	\$1,705
Global Drug Supply	8.1	\$334			\$1,078
Chemistry, Manufacturing and Controls (CMC)					
Analytics for Formulation (PARU)	8.8	\$110	\$385	\$541	\$1,022
Analytics for Process Chemistry (PARU)	3.3	\$59	\$182	\$271	\$511
Formulation (PARU)	5.8	\$101	\$329	\$484	\$1,561
Process R&D	16.3	\$922	\$1,283	\$860	\$8,372
Pre-Clinical Safety Evaluation					
Toxicology/Palliology	2.8	\$128	\$171	\$234	\$824
Microbiology	3.0	\$173	\$235	\$321	\$1,133
Other	0.4	\$18	\$25	\$34	\$120
Other Support Cost					
Discovery (Therapeutic Discovery)	2.9	\$214	\$128	\$170	\$869
Research Quality Assurance	3.3	\$138	\$18	\$316	\$900
Other Services Purchase	0.0				
	97.1			Total Internal	\$27,411
					\$44,708

Total Project:

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NO. 257 P. 13

CONFIDENTIALGPRD 2005 Plan
ABT/ST Base Program

<u>External:</u>		<u>Total Patients</u>		<u>Start</u>	<u>End</u>	<u>2005 Plan \$(000s)</u>
<u>Clinical Activities:</u>						
M02446 Lung Cancer Ph II	30			4/02	3/05	\$160
M02447 Breast Cancer Ph II	40			3/03	3/05	\$209
M02448 Colorectal Cancer Ph II	40			9/02	3/05	\$129
M02449 Renal Cancer Ph II	60			1/04	3/05	\$176
M01401 MD Anderson Leukemia Ph II	25			1/04	8/05	\$74
M01357 NCI Pediatric Drug safety and supply only Ph I	24			11/03	8/09	\$89
Investigator Initiated Abbott Investigated Collaboration Trials Ph II	0			6/04	5/05	\$42
<u>Subtotal Clinical Activities:</u>						
<u>Clinical Program</u>						
Global Drug Supply						\$0
Chemistry, Manufacturing and Controls (CMC)						\$10
PARD						
Other Support Cost						\$120
Global Project Management						\$988
<u>Total External</u>						
<u>\$120</u>						
<u>\$988</u>						
<u>2005 Plan \$(000s)</u>						
<u>\$1000s Chargeable</u>						
<u>Fixed</u>		<u>Overhead</u>		<u>Other</u>		
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NO. 257

P. 14

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GPRD 2005 Plan
Assessment Early PCA ABBT027

<u>Externals</u>		<u>Total Patients</u>	<u>Start</u>	<u>End</u>	<u>2005 Plan \$(000s)</u>
Clinical Activities:					
M01380 Phase II Hormone Native Ph II		200	9/02	4/05	\$2,082
Subtotal Clinical Activities:					\$2,082
Other Support Cost					\$160
Global Project Management					\$0
Other					\$0
					\$2,232
Total External					
<u>Internals</u>		<u>2005 Plan FTEs</u>	<u>\$000s/Chargeable</u>		<u>2005 Plan \$(000s)</u>
Clinical Program			<u>Payroll</u>	<u>Variable</u>	<u>Fixed</u>
Global Project Mgmt	1.4	\$189	\$17	\$13	\$387
Phase I Center Support	0.0				
European Clinical Organization	0.2	\$28	\$20	\$189	\$28
Data Management/Statistics	1.9	\$163	\$77	\$40	\$404
Global Drug Supply	0.0				\$169
Pre-Clinical Safety Evaluation					
Modeling	0.2	\$17	\$10	\$14	\$49
Other	0.3	\$28	\$16	\$22	\$79
Other Support Cost					
Discovery (Therapeutic Discovery)	0.2	\$24	\$9	\$12	\$59
Research/Quality Assurance	0.3	\$32	\$1	\$24	\$99
	6.0				\$1,242
Total Internal					
Total Project:					\$3,474

ABBT 0027258

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JUN. 17. 2005 2:22PM JAMES L TYREE

NO. 257 P. 15

CONFIDENTIALGPRD 2005 Plan
Atazanavir Base ABY627

<u>External:</u>		<u>Total Patients</u>		<u>Start</u>	<u>End</u>	<u>2005 Plan \$(000s)</u>
Clinical Activities:						
M03865 Combination Protonix/diclofenac and 027 safety dosing/eng Ph I		40		6/04	6/08	\$972
M41904 Phase III Long Term Safety Ph II		250		9/03	6/08	\$707
M00268 Ext for M00244 and M00211 Ph III		1000		12/02	5/09	\$2,400
M00244 VVW Hormonal/Prostate Cancer Ph III		941		6/04	8/05	\$11,344
Discovery		0		1/05	12/05	\$350
Cooperative Study with SWOG combo with docetaxel Ph III		0		2/05	12/07	\$400
Cooperative Study with ECOG Monotherapy Survival Ph III		0		7/05	12/11	\$900
MindWAY Outcomes Ph III		0		1/05	4/05	\$160
Subtotal Clinical Activities:						\$10,923
Clinical Program						\$10
Global Drug Supply						\$119
Pre-Clinical Safety Evaluation						\$929
Other Support Cost						\$376
Global Project Management (NDA Integrated Safety cost \$410 and GPO Product Launch \$400MM)						\$1,153
Global Outcome Research						\$10,509
Discovery						
Total External						
<u>Internal:</u>		<u>2005 Plan FTEs</u>		<u>2005 Plan \$(000s)</u>		
Clinical Program				<u>Fixed</u>	<u>Overhead</u>	<u>Other</u>
Global Project Mgmt	35.2			\$431	\$2,922	\$1,103
European Clinical Organization	3.6					
Phase 1 Center Support	1.2			\$26	\$119	
Data Management/Statistics	12.2			\$132	\$1,203	
Global Drug Supply	7.0			\$63	\$410	
Chemistry, Manufacturing and Controls (CMC)						
Formulation (PARD)	2.3			\$149	\$202	
Analytics for Formulation (PARD)	3.1			\$197	\$277	
Analytics for Process Chemistry (PARD)	1.0			\$95	\$130	
Perinatal & Advanced Drug Delivery	0.0					
Process R&D	4.0			\$308	\$209	
Pre-Clinical Safety Evaluation						
Toxicology/Pathology	0.1			\$7	\$9	
Metabolism	2.8			\$182	\$248	
Other	0.3			\$17	\$23	
Other Support Cost						
Discovery (Therapeutic Discovery)	6.1			\$221	\$301	
Research/Quality Assurance	2.8			\$14	\$214	
	61.3					
Total Project:					Total Internal	\$22,049
						\$12,358

ABBT 0027259

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JUN. 17. 2005

2:22PM

JAMES L TYREE

NO.257

P.16

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GPRD 2005 Plan
Amesentian Japan Registration AD1627

<u>Externals:</u>		<u>Total Patients</u>		<u>Start</u>	<u>End</u>	<u>2005 Plan \$1000s</u>
Clinical Activities:						
M02693 Vancouver Pharmacokinetic Study Prostate Cancer Ph I			48	6/04	6/05	\$89
Subtotal Clinical Activities:						\$89
Pre-Clinical Safety Evaluation						\$80
Other Support Cost						\$0
Japan Development Support						\$0
Other						\$0
Total External						\$767
<u>Internals:</u>		<u>2005 Plan FTEs</u>	<u>\$1000s/Chargeable</u>		<u>2005 Plan \$1000s</u>	
			<u>Variable</u>	<u>Fixed</u>	<u>Overhead</u>	<u>Other</u>
Clinical Program						
Phase 1 Center Support	1.1	\$162	\$39	\$25	\$112	\$327
Global Project Mgmt	0.1	\$21	\$7	\$2	\$12	\$42
European Clinical Organization	0.0					
Data Management/Statistics	1.0	\$114	\$7	\$12	\$118	\$251
Global Drug Supply	0.2	\$21	\$9	\$3	\$13	\$47
Japan Development Support	0.8	\$788	\$244	\$100		\$1,820
Pre-Clinical Safety Evaluation						
Toxicology/Pathology	0.1	\$7	\$3	\$4	\$9	\$20
Metabolism	1.9	\$216	\$83	\$128	\$172	\$509
Other Support Cost						
Discovery (Therapeutic Discovery)	0.4	\$49	\$29	\$16	\$21	\$109
Research Quality Assurance	0.2	\$28	\$9	\$1	\$21	\$59
	11.9				Total Internal	\$3,080
Total Project:						\$3,857

ABBT 0027260

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JUN. 17. 2005

2:22PM

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NO. 257

P.17

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GPRD 2005 Plan
Atreya's nonPCA Cancers (Pl U) ABT627

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ABBT 0027261

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**John Hancock Funding Agreement
Development Portfolio
Annual Progress Report (November 2004)**

ABT-627

- a) US New Drug Application submission is planned for December 2004.
- b) The Phase 3 pivotal trial M00-244 is continuing, with the February 2004 Independent Data Monitoring Committee recommending the trial be allowed to proceed
- c) Completion of enrollment for Phase 2 trial M01-366 occurred in May 2004.
- d) Enrollment continues for the Phase 1 pharmacokinetic study in Japan (M02-466). The second cohort (10 mg dose level) is currently enrolling, along with initiation of M03-593 to match patients from M02-466.
- e) The conduct of nine investigator-initiated studies continues. A total of 270 patients are enrolled as of October 13, 2004.
- f) A pharmacokinetic study of atrasentan in combination with docetaxel and prednisone (M03-655) has been initiated.

ABT-510

- a) Phase I: The last patients are complete in our Phase I Studies: M00-153 (Escalating Multiple Dose in Patients With Advanced Cancer); and M01-302 (Study Of Two Dose Schedules in Subjects With Advanced Cancer).
- b) Phase II:
 - Sarcoma - Enrollment complete; patients active (in treatment)
 - Renal - Enrollment complete; patients active
 - Lymphoma - Enrollment continuing, patients active
 - Lung (NSCLC) - Enrollment was stopped and the study discontinued after interim analysis failed to meet pre-specified criteria for efficacy. Patients are active.
- c) Phase III: Development and planning of Phase III Sarcoma program has been initiated, including the submission of a data package to the FDA and EMEA.
- d) Collaborations: A collaborative study is underway in metastatic melanoma.

ABT-751

- a) Phase I: Currently, one of two adult Phase I studies are open. A total of 106 patients have been enrolled in the two studies to date. Maximum tolerable doses (MTDs) have been determined for three of the four dose schedules covered by these studies.
- b) Phase II: Three of four Phase II trials are ongoing, with 207 patients enrolled in the four studies.
 - Renal - Enrollment complete, patients active
 - Lung - Enrollment complete, patients active
 - Colorectal - Enrollment nearly complete, patients active
 - Breast - Enrollment stopped and study discontinued after interim analysis failed to meet pre-specified criteria for efficacy; no patients active
- c) Collaborations:
 - The study in adult leukemia has been completed after enrolling 32 patients.
 - The study in pediatric cancers is ongoing with 44 patients enrolled.
 - Other collaborations are underway in colorectal cancer, lung cancer and prostate cancer, both with ABT-751 as a single agent, and in combination.

JUN. 17. 2005 2:22PM JAMES L TYREE

NO. 257 P. 19

**John Hancock Funding Agreement
Development Portfolio
Annual Progress Report (November 2004)**

ABT-773

On October 29, an Option Agreement was signed with Advanced Life Sciences, a private company based in Woodridge, Illinois, for an exclusive option to license ABT-773. The option expires on December 13, 2004. If the option is exercised, Advanced Life Sciences will have an exclusive license to develop, manufacture and commercialize ABT-773 for any human therapeutic uses. Territory rights are worldwide except Japan.

ABT-492

Over the past year, Abbott has re-contacted companies that have anti-infective businesses to inform them that ABT-492 is still available for out-license. Abbott has sent non-confidential summaries of the compound to several smaller companies that have responded with expressions of interest. Four companies have pursued additional information under confidentiality agreements; however no prospective licensees are currently showing strong interest in pursuing a transaction.

ABT-724

We are actively pursuing the out-licensing of ABT-724 and solicited interest from 57 companies. Initially a non-confidential summary was provided, and if further interest was expressed, a confidential summary was provided to a sub-set of those companies under an appropriate confidentiality agreement. Currently there are four companies with which there are ongoing discussions. Currently there are no bids which would compel us to move forward into further discussions / negotiations.

ABBT 0027263